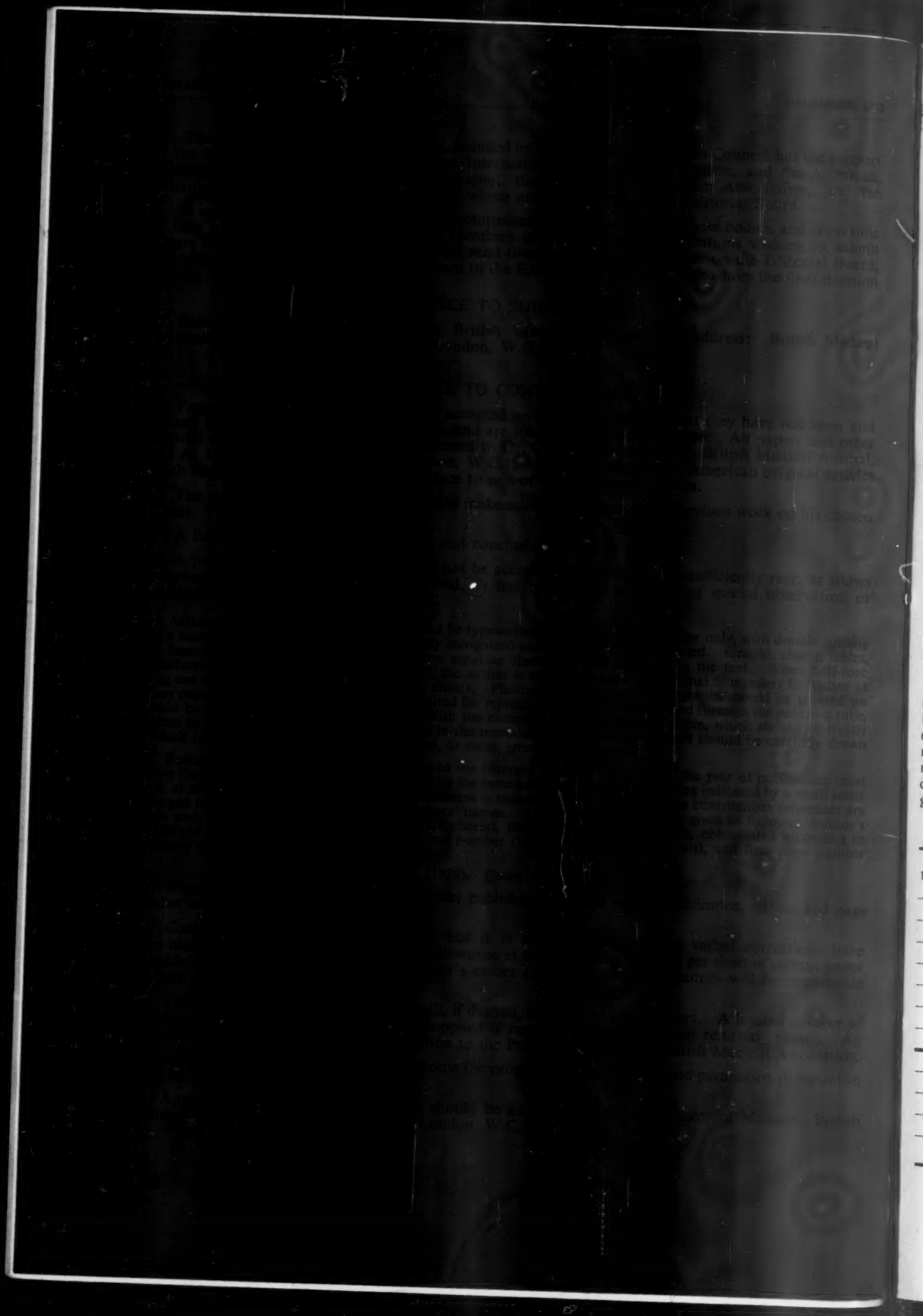
ANNALS OF THE RHEUMATIC DISEASES



EFFECTS OF ACTH AND CORTISONE ON THE ANAEMIA OF RHEUMATOID ARTHRITIS

BY

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The haematological effects of ACTH and cortisone on patients with rheumatoid arthritis have been described by Rosenthal and others (1950), Finch and others (1951), and Copeman and others (1952), but more information is needed.

Material

The present paper describes the haematological changes observed in a further twelve cases of rheumatoid arthritis during hormone therapy of 4 to 8 weeks' duration. All these patients had active polyarthritis of moderate severity associated with fever and increased sedimentation rates. Seven patients were treated with cortisone, the usual dose being 1,000 mg. the first week, 700 mg. the second week, and sufficient cortisone thereafter to maintain the clinical improvement of the first fortnight for a further 4 to 6 weeks. Five patients received ACTH in doses of between 45 and 760 mg. per week, sufficient being given to obtain and maintain clinical improvement (Table I). Analgesics, purgatives, etc., were allowed as needed and certain cases received iron preparations by mouth. Physiotherapy appropriate to their clinical condition was given. A thirteenth patient was investigated but did not receive hormone therapy.

Methods of Investigation

Before therapy was started, the venous blood and sternal marrow of each patient were investigated by standard methods, mostly as described by Dacie (1950). Haemoglobin (oxyhaemoglobin) was estimated colorimetrically. Total eosinophil counts were made in a double Fuchs-Rosenthal chamber, using one volume of blood with nine volumes of the modification described by Henneman and others (1949) of Randolph's fluid (Randolph, 1944). The erythrocyte sedimentation rate (E.S.R.) was measured by the technique of Westergren (1921). The serum iron was estimated by the method of Tompsett and McAllister (1949). Marrow from the manubrium sterni was concentrated (as described by Dacie, 1950) before the films were spread on slides. 500 cells were counted for each myelogram; a further 1,500 cells were counted to determine the eosinophil percentages. Sections were made of small marrow fragments by a modification of the method of White and others (1946).

After the start of therapy the blood counts and E.S.R.s were taken weekly. Marrow puncture was repeated once or twice during therapy at intervals which varied from 2 days to 5 weeks. The serum iron test was repeated in a few cases. Clinical improvement was assessed daily and, in greater detail, weekly.

TABLE I
DRUG AND WEEKLY DOSAGE (mg.) ADMINISTERED TO EACH PATIENT

Patient No.	Age	Sex	Week								Drug
			1	2	3	4	5	6	7	8	
1	60	M	1,000	700	671	500	500	400	—	—	Cortisone
2	29	M	1,000	700	600	600	800	—	—	—	Cortisone
3	27	F	1,000	700	700	600	600	600	600	600	Cortisone
4	56	F	1,000	675	375	350	450	775	800	625	Cortisone
5	38	F	1,000	700	562·5	480·5	—	—	650	600	Cortisone
6	50	F	1,000	700	562·5	375	350	350	275	350	Cortisone
7	23	F	1,000	700	600	450	450	200	275	300	Cortisone
8	53	F	625	700	640	450	—	—	—	—	ACTH (Armour)
9	41	F	360	100	47·5	70	100	70	—	—	ACTH (Wilson)
10	44	M	360	680	580	425	280	280	420	310	ACTH (Armour)
11	33	F	420	420	345	285	45	—	—	—	ACTH (Armour)
12	42	M	280	480	640	760	380	460	240	—	ACTH (Armour)

Observations

I. Before the Start of Therapy

Blood.—The initial red and white cell counts are shown in Tables II and III.

TABLE II

ABSOLUTE VALUES OF RED CELLS IN THIRTEEN CASES OF RHEUMATOID ARTHRITIS

Cells	Men (4)		Women (9)	
	Mean	Range	Mean	Range
Haemoglobin (g. per 100 ml. blood)	11·3	10·3-12·3	10·8	8·2-12·9
Red Cells (millions per c.mm.)	4·3	3·8- 4·8	4·2	3·6- 5·1
Packed Cell Volume (per 100 ml.) ..	36	31-39	36	31-38
Mean Cell Volume (cu.μ)	85	82-88	85	72-98
Mean Cell Haemoglobin ($\gamma\gamma$) ..	26	25-27	27	19-33
Mean Cell Haemoglobin Concentration (per cent.)	31	29-33	30	26-33
Reticulocytes (per cent. of red cells)	0·5	0·2- 1·0	0·6	0·2-1·8

TABLE III

LEUCOCYTE COUNT IN THIRTEEN CASES OF RHEUMATOID ARTHRITIS BEFORE THERAPY

		Mean	Range
Total Count (per c.mm.)		7,400	4,700-9,700
Neutrophils	(per cent.) ..	68	51·5-80·5
	(per c.mm.) ..	4,510	766-6,120
Lymphocytes	(per cent.) ..	22	9·5-33·5
	(per c.mm.) ..	1,600	940-3,030
Monocytes	(per cent.) ..	6·8	0-14
	(per c.mm.) ..	410	0-1,162
Eosinophils	(per cent.) ..	2·7	0-10
	(per c.mm.) ..	267	40-1,407
Miscellaneous	(per cent.) ..	0·3 plasma cells	0-2·0 plasma cells

In six cases the platelet count ranged from 239,000 to 388,000 per c.mm. (mean 318,000 per c.mm.).

In ten cases the serum iron varied from 37-135 μg. per 100 ml. serum (mean 72μg.).

In thirteen cases the erythrocyte sedimentation rate (Westergren) varied from 21 to 110 mm. in one hour (mean 57 mm.).

Marrow.—The findings in twelve patients before and after therapy are shown in Table IV, in comparison with six normal myelograms. Almost pure blood was obtained from the sternum of a thirteenth patient. Sections from eleven marrows showed blood only (1), hypoplastic marrow (3), erythroid hypoplasia (1), normal marrow (4), and myeloid hyperplasia (2).

TABLE IV

MEAN FIGURES OF MARROW COUNTS (CELLS PER CENT.)

Patients	Normal Series	Rheumatoid Arthritis		
		Before Therapy	During Cortisone	During ACTH
Number of Cases	6	12	7	5
Segmented neutrophils ..	14·4	12·7	16·4	10·3
Non-segmented neutrophils	32	36·7	34·1	35·8
Metamyelocytes	11·6	11·3	10·6	13·2
Myelocytes	6·4	4·2	4·4	5·0
Promyelocytes	0·8	0·5	0·6	0·4
Myeloblasts	0·6	0·8	0·4	0·3
Eosinophils*	0·9	2·02	0·94	1·71
Eosinophil metamyelocytes*	0·1	1·00	0·54	0·89
Eosinophil myelocytes* ..	0·8	1·10	0·54	0·83
Total eosinophils*	1·8	4·12	2·02	3·43
Basophils	0·1	0·1	—	—
Myeloid series	67·8	69·9	68·8	69·1
Lymphocytes	7·4	7·5	4·5	5·0
Prolymphocytes	0·03	0·1	0·1	—
Monocytes	1·1	2·7	1·7	1·8
Promonocytes	0·1	0·5	0·1	0·1
Monoblasts	—	0·01	—	—
Plasma cells	0·5	0·8	0·7	0·9
Proplasma cells	—	0·1	0·03	0·1
Plasmablasts	—	0·01	—	—
Normoblasts late	10·1	6·2	9·3	8·2
Normoblasts intermediate	8·9	5·6	8·5	7·0
Normoblasts early ..	2·6	3·4	4·1	4·1
Macronormoblasts ..	—	0·2	0·7	0·7
Proerythroblasts	0·5	0·9	0·5	0·5
Erythroid series	22·2	16·2	23·2	20·4
Haemocytoblasts	0·1	0·15	0·03	0·04
Reticulum cells	0·3	0·2	0·1	0·2
Megakaryocytes	0·3	0·3	0·3	0·4
Mitotic cells white ..	0·1	0·3	0·15	0·04
Mitotic cells red	0·3	0·4	0·1	0·4
Myeloid-erythroid ratio ..	3·2 : 1	4·8 : 1	3·8 : 1	3·7 : 1

*=2,000 cell counts.

Gastric Juice.—Analysis in ten cases showed that eight patients had no free acid in the fasting specimen and two had none in any specimen.

II. During and After Therapy

(*a*) *Changes in Red Cells.*—Seven cases received cortisone and five received ACTH. The changes in the red cells at 3 weeks are summarized in Table V and Student's "*t*" test applied. The absolute values calculated from these figures showed no significant change.

In the cases receiving cortisone the reticulocytes showed a small non-significant rise during the early weeks of therapy.

(*b*) *Changes in Blood Leucocytes.*—Six cases treated with cortisone showed a significant leucocytosis due to a significant neutrophilia after 3 weeks'

TABLE V

RED CELL CHANGES AT 3 WEEKS DURING HORMONE THERAPY

Drug	Estimation	Number of Cases	Mean change at 3 weeks	Standard Deviation of the Mean	Level of Significance (Student's "*t*")
Cortisone ..	Haemoglobin	6	+1·13 g. per cent.	2·76	0·05. Very slight significance
	Red cell count	6	+0·6 (millions per c.mm.)	2·34	0·1. Insignificant
	Packed cell volume	6	+2·67 per cent.	3·76	0·02. Slight significance
ACTH	Haemoglobin	5	+0·98 g. per cent.	2·18	0·1. Insignificant
	Red cell count	5	+0·46 (millions per c.mm.)	2·19	0·1. Insignificant
	Packed cell volume	5	+4·8 per cent.	2·96	0·05. Very slight significance

therapy. The lymphocytes, monocytes, and eosinophils showed no significant change (Table VI) at 3 weeks. Three cases showed no change in blood eosinophils, one showed an immediate, maintained fall, two showed an immediate fall and subsequent rise, one showed no immediate fall but a subsequent rise. "Falls" and "rises" imply at least a halving or a doubling of the initial count.

TABLE VI

CHANGES IN LEUCOCYTES AT 3 WEEKS DURING CORTISONE THERAPY

Cells	Number of Cases	Mean Change (per c.mm.)	Standard Deviation of the Mean	Level of Significance (Student's "*t*")
Total Leucocytes	6	+3,192	5·03	0·01 Significant
Neutrophils ..	6	+2,597	5·70	0·01 Significant
Lymphocytes ..	6	+601	1·85	Insignificant
Monocytes ..	6	+59	0·56	Insignificant
Eosinophils ..	6	−98	0·63	Insignificant

Leucocyte counts in the ACTH series were too incomplete for analysis, but two cases showed no change in the eosinophils and three showed an immediate fall followed by an "escape" to the original level whilst therapy continued.

(*c*) *Changes in Platelets.*—Not followed.

(*d*) *Changes in Serum Iron.*—Followed in seven cases.

Three men showed a mean of 84 μg. per cent. before and 86 μg. per cent. during hormone therapy (normal figures for these ages 106 μg. per cent.—Pirrie, 1952).

Four women showed a rise in the mean serum iron level from 48 μg. before to 74 μg. during therapy (normal figure for these ages 99 μg.).

(*e*) *Changes in E.S.R.*—All cases treated with cortisone showed a decrease: in one case to 35 mm./1 hr, in three cases to between 13 and 20 mm. and in three cases to below 13 mm. From 2 to 6 weeks were necessary for the maximum fall. Of five cases followed after therapy, two remained below their initial figure, two became raised above it, and one almost equalled it.

All cases treated with ACTH showed a decrease: in one case to 24 mm., in one case to 20 mm., and in three cases to below 13 mm. in 1 hour.

Of four cases followed after therapy, two remained below their initial figure and two rose above it.

(*f*) *Changes in Bone Marrow.*—These were studied by means of films and sections made from aspirated material, but no total counts were made because of their reported unreliability.

In seven cases treated with cortisone the myeloid series showed no significant change (Table IV, opposite, and Table VII, overleaf).

Considered separately, one patient (Case 6) showed a fall in the percentage figures due to a marked erythroid hyperplasia, and another (Case 2) showed a rise which was probably absolute as well as relative, because the percentage figures showed a "shift to the right" and the marrow section showed an increase in myeloid cells.

The total eosinophils showed a fall from 4·12 per cent. to 2·02 per cent. (mean figures), but the change is not significant.

The erythroid series showed no significant change in the series as a whole. Considered separately, two patients (Cases 4 and 6) showed an impressive increase (18·2 to 37·2 per cent. and 12·6 to 37·8 per cent., respectively).

The lymphocytes showed a fall from 7·5 to 4·5 per cent. (mean figures) which is significant at the 0·05 level.

TABLE VII
CHANGES IN BONE MARROW DURING HORMONE THERAPY

Drug	Cells	Number of Cases	Mean Change after Therapy (per cent.)	Standard Deviation of the Mean	Significance of the Change (Student's "*t*")
Cortisone ..	Myeloid cells	7	−0·97	3·42	Insignificant
	Total eosinophils	7	−1·91	1·21	Insignificant
	Lymphocytes	7	−3·00	1·07	0·05. Slight significance
	Erythroid cells	7	+5·37	4·35	Insignificant
ACTH	Myeloid cells	5	−0·36	5·77	Insignificant
	Total eosinophils	5	−0·94	1·71	Insignificant
	Lymphocytes	5	−2·72	2·15	Insignificant
	Erythroid cells	5	+4·80	4·00	Insignificant
Combined Series	Myeloid cells	12	−0·72	3·15	Insignificant
	Total eosinophils	12	−1·50	3·12	Insignificant
	Lymphocytes	12	−2·88	0·83	Significant at 0·02 level
	Erythroid cells	12	+5·13	1·04	Insignificant

In five cases treated with ACTH no significant change was found in the myeloid series, total eosinophils, lymphocytes, or erythroid series (Tables IV and VII).

One patient (Case 10) showed a myeloid hyperplasia. The total eosinophils fell from 4·12 to 3·43 per cent. (mean figures).

The lymphocytes fell from 7·5 to 5·0 per cent. (mean figures) and three patients (Cases 8, 9, and 12), showed an erythroid hyperplasia (15·6 to 28·4 per cent., 12·8 to 21·2 per cent., and 8·2 to 21·6 per cent. respectively) which was due mainly to an increase in the more mature normoblasts. The percentage of macronormoblasts increased slightly. The myeloid : erythroid ratio fell from 4·8 : 1 to 3·8 : 1 and 3·7 : 1 during cortisone and ACTH therapy respectively, a shift in the direction of normality (3·2 : 1).

If the cortisone and ACTH series are considered together (Table VII) the fall in the lymphocytes becomes more significant (at the 0·2 level) but the other changes remain insignificant.

The monocytes and their precursors showed a fall towards normal from 3·2 per cent. to 1·8 per cent. during cortisone therapy and to 1·9 per cent. during ACTH therapy (mean figures). The plasma cells showed no change.

(*g*) *Changes in Gastric Juice.*—Not followed.

Discussion and Analysis

The patients were selected for their willingness to co-operate and for severe polyarthritis. Anaemia was ignored in their selection. Thus the degree of anaemia found is not typical of rheumatoid arthritis in general, but only of cases selected for moderate duration and severity of arthritis. All the patients showed considerable improvement clinically if enough hormone was given, and it was endeavoured to keep the response constant from patient to patient by variation of the dose rather than to give a standard course of therapy and note the variation in the clinical response.

It is probably for this reason that the haematological variations do not appear to correspond as closely with clinical improvement as was noted by Finch and others (1951) in their hormone treated series, or by Nilsson (1948) in his iron treated cases.

I. Cases before Therapy.—As was to be expected from previous work, all the patients but one (Case 7) showed some degree of anaemia, the women showing lower values than the men. The anaemia was normocytic and slightly hypochromic, the reticulocytes and serum iron low, and erythropoiesis in the marrow normal or depressed, the most mature normoblasts being the most affected.

The blood neutrophils, lymphocytes, monocytes, and plasma cells were normal. The eosinophils were normal in all but one case. In the marrow, leucopoiesis varied from poor to active. No marked "shift to the left" was seen. The lymphocytes were normal. Plasmacytes were slightly increased, but the high figures of Hayhoe and Smith (1951), and of earlier continental workers, were not found, nor was there any increase in reticulum cells or megakaryocytes. There was a slight monocytosis (3·21 per cent. monocytes and

precursors) and an eosinophilia (4·12 per cent.). Because of the method of selection all patients had a raised erythrocyte sedimentation rate.

II. Effects of Therapy.—During therapy the haemoglobin, red cell count, and packed cell volume rose in six out of seven cases treated with cortisone. At 3 weeks the mean rise of the seven cases was just significant, but about half the gain had been lost by the 8th week. Five cases treated with ACTH showed similar changes at 3 weeks, but the smaller number of cases resulted in a lower degree of significance. It is probable that at least half the gain at 3 weeks was due to alterations in the plasma volume (see Robinson, 1943; Finch and others, 1951; Copeman and others, 1952). By 8 weeks doses of the hormone were in most cases small or had ceased and the apparent gain in the red cell mass at this time was probably a true one. The reticulocytes showed only a small gain and it seems probable that the large quantaties of blood removed by some investigators may have contributed to the height of the reported subsequent reticulocyte crisis.

Study of the erythroid series in the sternal marrow showed that in five of the twelve patients there was a well-marked erythropoietic response, and it is interesting that the mean initial haemoglobin of these 5 patients (four women and one man) was 1 g. per 100 ml. below the mean initial haemoglobin of the group. The mean haemoglobin of Cases 4, 6, 8, and 9 was 9·8 g. (mean for women, 10·8 g.). The haemoglobin of Case 12 was 10·3 g. (mean for men, 11·3 g.).

No correlation was noted between erythropoiesis and clinical response, probably because the dosage was varied widely to obtain a fairly standard clinical improvement, so that the most anaemic patients would need to respond most vigorously.

A moderate degree of anaemia has been shown to follow several hormone deficiencies which usually responded to treatment with the appropriate hormone (Gordon and Charipper, 1947; Daughaday and others, 1948). Similarly, in these cases of rheumatoid arthritis, the most anaemic patients reacted the most vigorously to cortisone and ACTH. It is probable that the hormones affected the disease processes which had inhibited normal erythropoiesis, so setting the marrow free to respond appropriately to the state of anaemia.

The similarity of the anaemia in infection and in rheumatoid arthritis has been pointed out by Kuhns and others (1950). Their six cases of polyarthritis showed a mean serum iron of 38 μg. (mean) and the response to intravenous iron was poor. Four women in our series showed a well-marked rise, from 48 μg. (mean) to 74 μg. (mean), on ACTH or cortisone, but did not attain the normal mean of 99 μg. Nor did three men in our series reach normality, which may be explained by the observation of Cartwright and others (1951) that ACTH and cortisone depress the serum iron level in dogs.

The changes seen in the leucocytes in the peripheral blood agreed closely with the observations of Finch and others (1951). The leucocytosis due to a neutrophilia was seen and was significant. No other change was significant, but in three cases there was an immediate eosinopenia and in three cases the initial eosinophil count was later more than doubled. Three of the five cases treated with ACTH showed an immediate eosinopenia with an "escape" to the original level in all.

The changes in the marrow are of considerable interest, though the smallness of the series limits their scientific value. The myeloid series as a whole showed no significant change after therapy, nor was there any "shift" to the left or right in the mean figures. Two cases showed increased leucopoiesis during therapy. Only three marrows were examined within 48 hours of starting therapy, but none showed the accumulation of mature myeloid cells found in mice by Antopol and others (1951).

The mean marrow eosinophil percentage showed no significant change, in spite of peripheral eosinopenia, in our combined ACTH and cortisone series, thus agreeing with Rosenthal and others (1950), Finch and others (1951), and Best and Samter (1951). The cortisone and ACTH series considered separately showed a change in the mean marrow eosinophils from 4·12 per cent. to 2·02 and 3·43 per cent. respectively.

Both cortisone and ACTH caused a similar and considerable fall in the marrow lymphocytes, which is significant at the 0·02 level for the combined series. This change has not been generally remarked in the human cases, possibly because the lymphocytes of the myelogram are usually considered to come from the blood. The work of Veeneklaas (1938), Blitstein (1945), Yoffey and others (1944-50) strongly suggests that the lymphocyte is also a true marrow cell.

The marrow monocytes fell to 1·8 per cent. during cortisone and to 1·9 per cent. during ACTH therapy; this phenomenon also has not been previously described.

No change was observed in the plasma cells, reticulum cells, or megakaryocytes, nor was there any correlation between plasmacytosis and the E.S.R. (Šiťaz and Kresánek, 1949).

The E.S.R. fell during therapy in all cases, especially between the 2nd and 6th weeks of therapy;

in half of the cases it fell to below 13 mm./1 hr. The degree of change indicated the degree of clinical improvement, but interpretation is obviously more difficult since Shock (1951) showed that ACTH reduces the E.S.R. in normal people.

Summary

(1) The blood, marrow, and gastric juice of thirteen cases of severe rheumatoid arthritis of moderate duration have been examined.

(2) Five cases received ACTH and seven received cortisone in sufficient dosage to obtain and maintain a considerable degree of clinical improvement.

(3) During the period of improvement serial examinations of the blood and marrow were made. The haemoglobin, red cell count, and packed cell volume rose in ten of the twelve cases to a degree significant at a low level, but half the gain had been lost by the 5th to 8th week, presumably on account of changes in the plasma volume caused by the therapy. The reticulocytes showed a small increase. Five of the twelve patients showed a well-marked erythroid response, which did not correspond with increased clinical response, but did correspond with the most severe degrees of anaemia. The response appeared to be due to release from the inhibiting effects of disease rather than a true " stimulation " of the marrow.

(4) Four women showed rises in the serum iron during therapy. Three men who started at a higher level showed no change. None achieved the normal level.

(5) During cortisone therapy there was a significant leucocytosis due to a significant neutrophilia. Changes in the other leucocytes were not significant, but about half the cases showed an immediate eosinopenia or a later eosinophilia. Three out of five cases treated with ACTH showed an immediate eosinopenia with subsequent " escape ". In the marrow, the myeloid series showed no significant change or shift, apart from increased leucopoiesis in two cases. The mean marrow eosinophils fell after cortisone and ACTH therapy, from 4·12 per cent. to 2·02 and 3·43 per cent. respectively. The change is not significant.

(6) ACTH and cortisone caused a significant fall in the marrow lymphocytes. The monocytes also fell, but did not reach significance.

(7) No change during therapy was noted in the plasma cells, reticulum cells, or megakaryocytes.

(8) The erythrocyte sedimentation rate fell in all cases during therapy, in half of them to less than 13 mm./1 hr (Westergren).

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Effets de l'ACTH et de la cortisone sur l'anémie de l'arthrite rhumatismale

RÉSUMÉ

(1) On a examiné le sang, la moelle osseuse, et le suc gastrique dans treize cas d'arthrite rhumatismale grave et d'ancienneté modérée.

(2) Cinq cas ont reçu de l'ACTH et sept autres de la cortisone en doses suffisantes pour obtenir et maintenir une amélioration clinique considérable.

(3) Au cours de la période d'amélioration on a procédé à une série d'examens du sang et de la moelle. Dans dix cas sur douze l'hémoglobine, le nombre des globules rouges, et le volume globulaire ont accusé une augmentation signifiante, sans toutefois dépasser un niveau bas. La moitié de ce gain fut reperdue entre la 5me et la 8me semaine, probablement à conséquence des altérations du volume plasmatique provoquées par le traitement. Il y a eu une légère augmentation du

chiffre des réticulocytes. Cinq malades sur douze ont manifesté une réponse érythroïde bien marquée correspondante à la grande sévérité de l'anémie et non pas à l'intensité de l'amélioration clinique. Cette réponse a paru résulter de la suppression des effets inhibiteurs de la maladie plutôt que d'une vraie " stimulation " de la moelle.

(4) Chez 4 femmes le chiffre du fer sérique a accusé une augmentation, tandis que chez 3 hommes, chez qui ce chiffre avait été plus élevé au commencement, on n'a observé aucune modification. Personne n'a atteint un taux normal.

(5) Pendant la thérapie à la cortisone il y a eu une leucocytose signifiante due à une neutrophilie signifiante. Les autres déviations leucocytaires n'ont pas été signifiantes, mais dans prés de la moitié des cas on a observé une éosinopénie, suivie d'un " échappement ". Dans la moelle, la lignée myéloïde n'a accusé aucune modification ni déviation signifiante, à l'exception de deux cas de leucopoyèse augmentée. Les éosinophiles de la moelle sont tombés après le traitement par la cortisone et l'ACTH de 4,12% à 2,02% et 3,43% respectivement. Cette altération n'est pas signifiante.

(6) L'ACTH et la cortisone ont provoqué une chute signifiante des lymphocytes myéloïdes. Il y a eu aussi une diminution des monocytes, pas assez prononcée pour être signifiante.

(7) Au cours du traitement on n'a pas observé d'altérations en ce qui concerne les plasmocytes, les réticulocytes, et les mégacaryocytes.

(8) Il a eu une diminution de la vitesse de sédimentation dans tous les cas traités; dans la moitié de ces cas elle a été en dessous de 13 mm. en 1-re heure (Westergren).

Efectos de la ACTH y de la cortisona sobre la anemia de la artritis reumatoide

SUMARIO

(1) Se ha examinado la sangre, la médula ósea, y el jugo gástrico en trece casos de artritis reumatoide grave y de duración moderada.

(2) Cinco casos recibieron ACTH y siete cortisona en dosis suficientes para obtener y mantener una mejoría clínica considerable.

(3) Durante el período de mejoría se ha procedido a series de investigaciones de la sangre y de la médula. En diez de los doce casos las cifras de la hemoglobina, de los eritrocitos, y del volumen corpuscular, aunque siempre bajas, aumentaron de manera estadísticamente significante. La mitad de esta ganancia fué perdida entre la quinta y la octava semana, probablemente a consecuencia de las alteraciones del volumen plasmático causadas por el tratamiento. El número de los reticulocitos estuvo algo aumentado. Cinco de los doce enfermos manifestaron una reacción eritroide bien acentuada que no correspondía a la intensidad de la mejoría clínica sino a la gran severidad de la anemia. Esta reacción pareció resultar más bien de la supresión de los efectos inhibidores de la enfermedad que de la auténtica " estimulación " medular.

(4) En 4 mujeres las cifras del hierro en el suero aumentaron; en 3 hombres estas cifras, más altas al principio, quedaron sin cambiar. En ninguno el hierro alcanzó valores normales.

(5) Durante el tratamiento con la cortisona se observó una leucocitosis significante debida a una neutrofilia significante. Otras desviaciones leucocitarias no tuvieron importancia, pero en cerca de la mitad de los casos hubo una eosinopenia, seguida de " fuga ". En la médula, la serie medular no reveló alteraciones o desviaciones significantes, a excepción de la leucopoyesis aumentada en dos casos. Los valores de los eosinófilos bajaron después del tratamiento con cortisona y con ACTH de 4,12% a 2,02% y 3,43% respectivamente. Estas alteraciones no tienen significancia estadística.

(6) La ACTH y la cortisona motivaron una baja significante de las cifras de los linfocitos medulares. Las cifras de los monocitos también bajaron, sin alcanzar una diferencia significante.

(7) Durante el tratamiento no se observó alteraciones en los plasmocitos, reticulocitos, o megacariocitos.

(8) La velocidad de sedimentación durante el tratamiento bajó en todos los casos, descendiendo debajo de 13 mm./1-ra hora (Westergren) en la mitad de ellos.

LA POLYARTHRITE MASCULINE

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Les aspects cliniques et radiologiques de la polyarthrite chronique évolutive sont multiples. Ce fait semble être en partie sous l'influence du processus inflammatoire qui peut diminuer d'intensité ou disparaître à n'importe quelle phase de la maladie; mais une étude de cas masculins permet de soupçonner que l'âge, c'est à dire un des facteurs essentiels du terrain, joue un rôle dans la détermination du type d'altérations radiologiques.

L'élément inflammatoire de la polyarthrite est, classiquement, la prolifération synoviale; l'altération radiologique à un stade avancé est l'atrophie ou la destruction des extrémités osseuses. Chez l'homme, cet élément inflammatoire peut revêtir plusieurs aspects: proliférations, épanchements plus ou moins abondants, ou épaississements durs. Il nous a paru intéressant de rechercher s'il y avait une relation entre l'élément clinique constaté et le type d'altérations radiologiques.

Matériel

Notre étude est basée sur 48 cas dont l'ancienneté est très variable (de quelques mois à 45 ans); neuf de ces cas ont été suivis pendant une période qui est pour certains de plus de 15 ans, ce qui présente un intérêt, car, il a été ainsi possible de connaître la réponse aux diverses thérapeutiques. Le nombre de nos cas est peu élevé mais nous n'avons voulu retenir que les dossiers comprenant une radiographie des articulations sacro-iliaques (pour éliminer le diagnostic de spondylarthrite) et un cliché d'une des articulations atteintes: hanche, poignet, etc. Or, comme il s'agit de malades de clientèle privée, ce sont surtout les cas sévères, avec lésions destructives qui ont été radiographiés. Nous ne pouvons donc pas présenter de pourcentage des différentes formes cliniques, car les cas à poussées fluxionnaires ou à petits épanchements qui n'entrainent qu'une invalidité soit temporaire, soit discrète, n'ont pas subi d'examen radiologique.

Fréquence.—La proportion des cas masculins et féminins est très différente. Fletcher et Rowley (1952) donnent par exemple un homme pour deux femmes; nous-mêmes avons indiqué le pourcentage de 20 pour cent. de cas masculins. Cette différence nous semble due à la définition même de la polyarthrite. Dans notre statistique nous n'avions tenu compte que des cas polyarticulaires avec atteinte symétrique; nous éliminions alors en particulier les oligo-arthrites. Le diagnostic de polyarthrite chez l'homme doit être fait avec plus de précautions que chez la femme en raison de la fréquence des spondylarthrites à début périphérique et de l'existence de la goutte polyarticulaire chronique; de plus, il ne faut pas oublier qu'il s'agit non d'une affection dont l'étiologie est connue, mais d'un syndrome clinique et radiologique dont les limites sont quelquefois difficiles à définir. Toutefois, le rhumatisme inflammatoire localisé aux articulations périphériques semble être beaucoup plus fréquent chez l'homme que l'on ne le pensait.

Antécédents.—Onze cas seulement présentaient au début de leur affection un facteur déclenchant net. Il s'agissait le plus souvent d'antécédents infectieux; abcès dentaires, amygdalite, blennorragie (un cas).

Divers auteurs ont noté que la polyarthrite de l'homme était souvent consécutive à une gonococcie. Selon nous, il n'existe pas de véritable polyarthrite gonococcique ou blennoragique l'infection joue selon nous un rôle de "facteur déclenchant". De plus, nous avons noté, lors de blennorragie, des douleurs articulaires, accompagnées ou non de gonflement, localisées surtout au niveau des membres inférieurs, mais généralement ces manifestations sont de courte durée et ne laissent habituellement pas de séquelles; nous pourrions faire la même remarque pour les poussées articulaires fugitives qui suivent une angine. Ces poussées réagissent rapidement aux antibiotiques.

Trois cas ont débuté aussitôt après une fracture articulaire: ce fut l'articulation traumatisée qui présenta d'abord les signes inflammatoires. Un sujet ressentit les premiers symptômes les jours qui suivirent une fracture du crâne. Dans un cas observé récemment, la polyarthrite débuta aussitôt après un ictus, qui laisse actuellement pour séquelle une monoplégie.

Les poussées ultérieures sont déclenchées soit par le même facteur, soit par d'autres. Il est à noter que des cas de polyarthrite ayant débuté avant 20 ans et stabilisés les années suivantes ont présenté à nouveau une poussée quelquefois sévère quand

les malades atteignirent la quarantaine. Or la plupart de nos cas de polyarthrite chronique évolutive ont débuté entre 30 et 50 ans, l'âge est donc un facteur déclenchant. Le terrain joue donc un rôle important; comme nous le verrons plus loin, les altérations notées à partir de cet âge sont destructives.

Age de Début.—Cinq de nos cas ont débuté entre 16 et 20 ans; la plupart ont débuté entre 30 et 50 ans (28 cas), un de nos cas après 70 ans.

Symptômes de Début

Premières Localisations

Atteinte Monoarticulaire.—La maladie débuta par une atteinte monoarticulaire dans six cas. Il s'agissait d'un genou, d'un poignet, d'une épaule ou d'un coude et cette atteinte persistante est restée monoarticulaire pendant une période variant de quelques mois à 6 ans.

L'atteinte de l'épaule fut la seule localisation de début dans deux cas; ceci est à souligner, car bien souvent en présence de douleurs et de raideur de l'épaule, le diagnostic de périarthrite a été fait le plus fréquemment. Ce diagnostic de périarthrite semblait être confirmé par la constatation de signes d'arthrose cervicale, car cette association est classique; or, la plupart de nos sujets ont 40 ou 50 ans, période de la vie où il est déjà banal de trouver une raideur du cou, des affaissements discaux, et quelques ostéophytes au niveau de la région cervicale inférieure. Il faut en présence d'une périarthrite de l'épaule pratiquer une sédimentation globulaire et, si les symptômes cliniques persistent plusieurs mois, il faut examiner à nouveau soigneusement toutes les articulations et en particulier les poignets.

Dans trois autres cas, les deux épaules furent atteintes simultanément; le diagnostic de polyarthrite doit être alors envisagé dès le début car la simultanéité de deux périarthrites est exceptionnelle. La périarthrite à bascule existe, mais il faut être prudent devant un tel diagnostic.

Atteinte Oligo-Articulaire.—Le début fut oligo-articulaire dans trente cas. Il s'agissait soit d'une atteinte symétrique, soit d'une atteinte de deux, trois ou quatre articulations non symétriques et l'affection est restée pauci-articulaire pendant de très nombreuses années (dans un de nos cas elle l'est restée pendant 31 ans) pour devenir ensuite poly-articulaire et être alors généralement symétrique. Le problème de l'oligo-arthrite sera étudié au diagnostic différentiel.

Atteinte Polyarticulaire.—Le début fut poly-articulaire dans dix de nos cas et dans la moitié de ceux-ci, il s'agissait de poussées fluxionnaires, c'est à dire de manifestations intermittentes.

Signes Généraux.—Les signes généraux de début furent nets dans 32 cas sur 48. Il s'agissait soit de fièvre, soit d'amaigrissement, soit des deux le plus souvent. Ces signes de début existaient, que l'atteinte soit localisée ou polyarticulaire. La polyarthrite de l'homme s'accompagne donc fréquemment d'une atteinte de l'état général; par contre celui-ci n'est pratiquement jamais modifié à la phase de début de la spondylarthrite ankylosante dans les cas qui ne présentent que des symptômes sacro-iliaques ou rachidiens (Jacqueline *et al.*, 1952).

L'étude des symptômes de début met en évidence que le tableau clinique se constitue soit rapidement soit en de nombreuses années, c'est dire que l'évolution est variable et les tableaux cliniques multiples.

Éléments Articulaires Inflammatoires et Altérations Radiologiques

L'étude radiologique a été faite, d'une part d'après l'articulation ou les articulations dont les clichés étaient nécessaires pour faire un bilan orthopédique, et d'autre part d'après les poignets et les mains, et c'est essentiellement les modifications constatées au niveau de ceux-ci que nous rapportons ici. Nous indiquerons simplement les quelques particularités que nous avons pu noter au niveau des autres articulations.

Nous avons classé nos cas suivant leur âge au moment de l'observation et nous avons noté que l'élément articulaire inflammatoire et le type d'altérations radiologiques dépendent de celui-ci. Certains sujets ont débuté jeunes leur polyarthrite, mais ils n'ont été examinés par nous que lorsqu' ils avaient atteint 50 ou 60 ans, le processus inflammatoire ayant persisté ou étant réapparu après une longue période de stabilisation; les altérations radiologiques notées alors nous paraissent beaucoup plus difficiles à analyser (Fig. 3).

(1) Forme ankylosante de l'adulte jeune, sans destructions osseuses (Nous éliminons de notre étude les polyarthrites de l'enfance).—Quatre de nos cas de polyarthrite ont entre 18 et 26 ans. Le mode de début fut peu différent de celui des autres cas. L'atteinte est actuellement diffuse; dans deux cas la région cervicale est atteinte et chez l'un de ceux-ci, il existe une cyphose dorsale avec raideur importante. Bien qu'il s'agisse de cas évoluant depuis 6 ou 7 ans, nous n'avons noté, au niveau du rachis, que des altérations inter-apophysaires; il n'existe ni ponts osseux ni altérations des sacro-iliaques.

La plupart des articulations atteintes étaient très enraidies et quelques unes bloquées. Dans un cas les douleurs ne furent jamais vives bien que l'examen révèle des blocages articulaires. Ce fait clinique est à rapprocher de la relative indolence de nombreux cas de polyarthrite de l'adolescence et de l'enfance. Les modifications des mains sont différentes de celles de la polyarthrite habituelle. Les téguments de couleur légèrement violacée étaient froids et

se laissaient mal décoller des plans profonds; les articulations inter-phalangiennes distales étaient moins volumineuses mais très enraidies; le malade ne pouvait ni fermer ni étendre complètement les doigts. La palpation des articulations inter-phalangiennes révèlait un épaississement dur des tissus. Les déviations étaient discrètes.

L'atrophie musculaire, masquée en partie par l'épaississement dur de la peau, était prononcée. Dans un cas, le gonflement du poignet était manifeste, et la peau était tendue et chaude, mais nous n'avions pas cette impression "amadou" de tuméfaction molle qui caractérise la prolifération.

La radiographie des poignets bloqués nous a révélé une image d'*ankylose osseuse sans destructions*. Cette ankylose était soit localisée à certaines articulations du poignet soit diffuse. Fig. 1 montre que le carpe est devenu un véritable bloc osseux, mais qu'il a conservé une hauteur normale; les os du carpe et du métacarpe ont conservé des rapports normaux, il n'y a donc pas eu de destruction osseuse; il n'existe pas de zône de condensation. Sur ce cliché, nous ne notons pas de troubles de structure. Chez un autre malade, il existait une porose importante.

Les articulations inter-phalangiennes distales qui ont conservé un certain degré de mobilité présentent une légère sclérose de certaines articulations qui sont prolongées par des formations osseuses; celles-ci sont quelquefois difficile à différencier des altérations dites arthrosiques; mais il existe une porose nette.

La vitesse de sédimentation était élevée dans trois des cas; elle était normale dans le quatrième alors que la douleur articulaire était vive et que la raideur augmentait. La vitesse de sédimentation n'était donc pas en rapport avec l'état clinique; il est à noter que, dans ce cas, il n'existait pas de proliférations (ce manque de concordance entre l'état clinique et la vitesse de sédimentation a été noté aussi dans des cas de spondylarthrite). Le processus ankylosant sans destructions osseuses ne s'accompagne donc pas toujours de modifications de la vitesse de sédimentation (Jacqueline *et al.*, 1951).

(2) Forme proliférative et destructive du sujet de plus de 30 ans (Généralement entre 40 et 50 ans). —Trente cas présentent des proliférations typiques analogues à celles considérées comme classiques. Vingt de ces cas sont sévères et l'atteinte très diffuse est généralement symétrique. Elle s'accompagne de raideur plus ou moins importante avec des déviations et des subluxations quelquefois très marquées.

Les radiographies révèlent dans ces cas sévères dont la durée d'évolution était pour quelques uns de 2 ou 3 ans seulement, des *lésions destructives* (Fig. 2) ou *atrophiques* (Fig. 4) extrèment importantes. Les os du carpe présentent des contours déchiquetés à l'emporte-pièce. Ces altérations sont très marquées à l'extrèmité inférieure du radius et dans la région du carpe qui est en rapport avec le deuxième métacarpien, plus particulièrement le trapèzoïde. Le carpe est généralement diminué de hauteur; mais c'est surtout la distance radius-deuxième métacarpien qui est le plus nettement réduite, et il en résulte généralement une déviation radiale du carpe plus ou moins marquée qui s'oppose à une déviation cubitale des articulations métacarpo-phalangiennes.*

Les troubles de structure sont très marqués; il existe des zones de condensation qui bornent les surfaces articulaires plus ou moins régulièrement; il est intéressant de noter que la condensation et la destruction des surfaces articulaires sont concomitantes.

Le processus destructif peut soit être localisé à la *Zone juxta-articulaire* qui s'amenuise, et alors la destruction ne s'accompagne pas de condensation, soit s'étendre ou être localisé à la *surface articulaire*. Au niveau des phalanges et des metacarpiens la destruction des surfaces articulaires peut être le stade avancé de destructions qui ont *débuté* dans la zone juxta-articulaire. Par contre, au niveau d'autres articulations et en particulier des hanches, la destruction est d'emblée localisée à la surface articulaire; il n'existe pas de destruction juxta-articulaire. Les altérations radiologiques sont donc différentes suivant les articulations.

Il existe par ailleurs des phénomènes de lyse dans certains cas de polyarthrite dont nous ne parlons pas ici et que nous n'avons notés que chez la femme.

Or, pour les hanches, les zones de destruction correspondent aux zones d'appui normales puis pathologiques. Il nous parait en être de même pour les poignets: destruction et condensation semblent être en rapport avec les zones ou s'exercent les pressions (Figs 2 et 5). Celles-ci sont: en partie sous la dépendance de la contracture musculaire. Les zones de condensation paraissent plus marquées chez l'homme que chez la femme, alors que généralement l'ostéoporose, comme nous l'indiquons plus tard, est relativement discrète chez l'homme alors qu'elle est intense chez la femme. Outre ces zones de condensation, il existe des géodes soit dans le voisinage des zones détruites, soit dans les épiphyses des doigts à la limite des pourtours articulaires. Ces géodes sont quelquefois difficiles à différencier de celles observées dans la goutte.

Ces altérations existent au niveau des autres articulations et en particulier des hanches; elles sont intenses au

* Nous n'avons pas noté de dislocation du poignet, avec ou sans destruction, dans nos cas de polyarthrite; celle-ci n'est pas rare dans les cas de polyarthrite chronique évolutive féminine.

Fig. 1.—Polyarthrite de 9 ans d'évolution chez un homme de 24 ans. Atteinte des deux poignets à l'âge de 16 ans.

Le poignet droit est bloqué en extension. La palpation révèle un épaississement dur; le cliché montre une ankylose osseuse du carpe sans destructions. Les vestiges des surfaces articulaires indique que la hauteur des anciens interlignes n'a pas été modifiée. Aucun trouble de la structure.

Fig. 2.—Polyarthrite masculine de 9 ans d'évolution chez un homme de 65 ans, ayant débuté à 56 ans. Forme sévère, très proliférative.

Poignet droit très enraidi: lésions destructives marquées, en particulier de la base du radius, aspect déchiqueté des contours. Les condensations sont importantes.

Fig. 3.—Polyarthrite de 40 ans d'évolution chez un homme de 55 ans. La polyarthrite a débuté à l'âge de 13 ans par petites poussées qui ont évolué pendant 10 ans. Puis le malade a présenté une nouvelle poussée vers 50 ans.

Le poignet gauche est ankylosé en rectitude; la radiographie révèle une ankylose de la première rangée du carpe avec le radius (ceci est à rapprocher de la Fig. 1) et des zones de condensation surtout importantes entre la première et la deuxième rangée des os du carpe. A noter des troubles importants de la structure, notamment à l'extrémité inférieure du cubitus.

Fig. 4.—Polyarthrite sévère de 4 ans d'évolution chez un homme de 64 ans. Le poignet droit est très enraidi; il existe à ce niveau des proliférations molles et très douloureuses à la palpation. Le cliché révèle une atrophie extrêmement importante de tous les os du carpe; celui-ci est considérablement diminué de hauteur à tel point que la styloïde radiale est très près de la base du deuxième métacarpien.

niveau des genoux alors que dans la polyarthrite féminine nous constatons une porose, un pincement, des déplacements, mais les destructions à ce niveau sont discrètes.

L'ostéoporose précède la destruction, le pincement articulaire est précoce. Les déplacements sont, dans cette forme, généralement en rapport avec les destructions qui sont d'apparition rapide. Mais dans quelques cas, les surfaces articulaires sont peu altérées mais les rapports de celles-ci très modifiés; ceci semble alors dû à une atteinte élective de l'appareil ligamentaire de maintien par le processus inflammatoire et une action prédominante des muscles fléchisseurs de la main par exemple.

(3) Forme hydarthrodiale survenant généralement à partir de 40-50 ans.—Dans sept cas il s'agit d'une atteinte diffuse des mains, mais pas toujours symétrique. Au niveau du poignet le gonflement articulaire se présente sous la forme de bosses plus ou moins marquées et il peut être opposé à l'empâtement diffus des proliférations. La palpation révèle qu'il s'agit de petits épanchements, et ceux-ci peuvent quelquefois être associés chez un même sujet à des proliférations; mais chez ceux de notre étude, il ne s'agissait que d'épanchements purs. La mobilité est conservée. La radiographie peut montrer soit un poignet normal soit une légère ostéoporose. Il est courant de remarquer que malgré l'importance de l'épanchement les déviations sont peu marquées. L'épanchement doit dilater les différents culs-de sacs synoviaux sans modifier l'appareil de maintien. De plus la douleur et la contraction musculaire sont moins prononcées.

Ces petits épanchements peuvent exister au niveau de toutes les articulations et, en particulier, des genoux. Dans cette forme, l'atteinte des hanches est extrèmement rare.

L'évolution de cette forme peut-être soit continue avec de petites poussées, soit, le plus souvent, intermittente. Cette forme, dont le pronostic nous paraît relativement bénin et dans laquelle la sédimentation est souvent élevée, est, d'autre part, très rebelle à la plupart des thérapeutiques.

" *L'hydropisie polyarticulaire chronique* " (Forestier et Certonciny, 1944; Forestier *et al.*, 1949) touche surtout les grosses articulations et d'une manière symétrique; les mouvements sont peu limités sauf par le volume des épanchements. Il existe parfois de la laxité articulaire mais pour ainsi dire jamais d'attitudes vicieuses importantes.

Nous classons cette affection dans le cadre des rhumatismes inflammatoires mais nous ne savons si elle doit être distinguée de la polyarthrite surtout de la forme hydrarthrodiale. Les localisations sont certes différentes mais l'évolution de certains cas d'hydropisie polyarticulaire suivis pendant de nombreuses années ont révèlé que cette affection pouvait évoluer vers une plus grande diffusion, qu'il pouvait s'y associer plus ou moins tardivement des proliférations et des altérations destructives.

Fig. 5.—Polyarthrite de 27 ans d'évolution, chez un homme de 58 ans; cette polyarthrite sévère continue à évoluer.

Poignet droit bloqué: lésions destructives moins importantes que sur la Fig. 2, ankylose osseuse de l'articulation radio-cubitale inférieure non soumise à des pressions, déviation radiale du poignet.

Les divers rhumatismes inflammatoires ne sont que des syndromes cliniques. Peut-être ne s'agit-il que de formes cliniques d'une seule maladie. (Nous mettons à part la spondylarthrite ankylosante.)

(4) Polyarthrite douloureuse du sujet de plus de 70 ans.—Deux de nos cas (nous rappelons que nous n'avons conservé pour ce travail que des dossiers complets) ont présenté un tableau de douleurs extrèmement vives, rapidement diffuses avec atteintes de l'état général—fièvre et amaigrissement. Dans ce tableau l'atteinte des hanches et surtout des épaules prédominait.* Actuellement, après un début bruyant qui date de 2 à 3 ans, l'affection semble se stabiliser. *A l'examen:* la douleur est vive à la palpation et à la mobilisation, mais il n'existe aucune prolifération synoviale, la radiographie ne révèle aucune altération, la raideur douloureuse des épaules semble surtout être la cause de l'invalidité relative de cas malades.

* Dans une prochaine publication, nous décrirons avec le Docteur A. Certonciny un tableau localisé aux articulations rhizoméliques.

En résumé, l'âge du malade nous paraît jouer un rôle dans le type d'altérations radiologiques que nous pouvons constater au niveau des articulations où le processus rhumatismal a été sévère et persistant: *chez l'homme jeune* la polyarthrite aboutit à une ankylose par transformation osseuse des éléments mous articulaires; chez l'homme de plus de 30 ans elle donne des destructions et des atrophies osseuses.*

Cette ankylose du jeune pose un problème nosologique. La différence essentielle entre le type d'altérations radiologiques constatées au niveau des membres dans la spondylarthrite et celles constatées dans la polyarthrite était pour nous, que les premières, à leur stade avancé, étaient une ankylose et que celles de la polyarthrite étaient une destruction (Forestier *et al.*, 1951). Or cette étude met en évidence que la polyarthrite du jeune peut aussi donner une ankylose osseuse sans destructions.†

Néanmoins nous continuerons à considérer la polyarthrite et la spondylarthrite ankylosante comme deux entités cliniques différents. La spondylarthrite présente certains caractères cliniques (localisation rachidienne et surtout évolution ascendante, iritis, absence de nodules fibreux, même dans les cas avec atteinte des membres) et radiologiques (stade 1 et 2 des articulations sacro-iliaques, Forestier et Metzger, 1939, syndesmophytes ou ponts osseux juxta-discaux, absence d'altérations du type destructif dans les cas qui évoluent chez des sujets de plus de 30 ans),‡ caractères qui lui appartiennent en propre. De plus, les localisations périphériques qui peuvent survenir au cours de la spondylarthrite sont différentes de celles de la polyarthrite: l'atteinte des mains et surtout des poignets et des coudes est extrèmement rare dans la spondylarthrite alors que l'atteinte des articulations acroméliques, même chez le jeune, est habituelle. L'ankylose chez le jeune s'observe donc sur des articulations différentes.

Autres Notions Cliniques

Des adénopathies furent notées dans huit cas (syndrome de Chauffard et Ramond), et des nodules fibreux dans neuf autres cas. Ceux-ci nous semblent donc plus frèquents que chez la femme.

Il existait une maladie de Dupuytren chez deux sujets présentant une polyarthrite.

Surtout nous avons noté dans sept cas, dont trois jeunes, des troubles trophiques importants: épaississement des téguments qui sont violacés et froids, alors que l'amincissement de la peau, phénomène fréquent chez la femme, n'a pas été constaté dans notre série. Les mains de nos malades peuvent évoquer dans certains cas le diagnostic de sclérodermie.

La polyarthrite de l'homme est sévère; sept de nos cas étaient grabataires, 31 ne pouvaient se déplacer qu'avec difficulté et ne pouvaient fournir un travail régulier; il s'agissait de deux sujets jeunes à forme ankylosante extensive et les autres plus âgés avec des proliférations et des destructions; les cas avec petits épanchements même multiples, n'étaient pas invalides.

De plus, la polyarthrite de l'homme semble plus rebelle aux diverses thérapeutiques que celle de la femme; et même les traitements hormonaux (cortisone et ACTH) paraissent soit donner des résultats moins spectaculaires, soit, après l'arrêt de ceux-ci, déclencher des poussées plus vives que chez la femme. La forme hydarthrodiale est, elle aussi, rebelle, mais, comme nous venons de l'indiquer, son pronostic est beaucoup plus favorable.

Diagnostic Differentiel

Le diagnostic ne se pose pratiquement qu'à la phase de *monoarthrite* ou d'*oligo-arthrite*. Dans le premier cas, s'il s'agit d'une atteinte persistante de l'épaule, le diagnostic de périarthrite non calcifiante ou adhésive ne doit pas être maintenu pendant plusieurs mois ou années; s'il s'agit d'une autre articulation périphérique, le diagnostic de monoarthrite infectieuse, surtout tuberculeuse, est généralement fait, et nous voyons trop de malades dont le diagnostic est suivi d'un acte chirurgical, alors qu'au moment de l'intervention il n'existait que des signes banaux inflammatoires: douleurs, gonflement, raideur, et légère ostéoporose. La preuve de l'infection tuberculeuse par la biopsie et par l'inoculation au cobaye doit être faite avant de décider une immobilisation plâtrée ou une résection des extrémités osseuses. Une irrégularité des surfaces articulaires nous paraît être extrèmement rare à la phase de monoarthrite d'un rhumatisme inflammatoire.

En présence d'atteinte pauci-articulaire de type inflammatoire, surtout si celle-ci est localisée aux membres inférieurs et en particulier aux pieds et aux chevilles, il faut éliminer:

* La polyarthrite de l'enfance donne aussi des ankyloses mais les épiphyses qui sont malléables en raison de l'âge et qui subissent en raison de la contracture musculaire des pressions importantes sont déformées. De plus, les attitudes vicieuses de la polyarthrite de l'enfance sont précoces et la pression s'exerce dans des conditions anormales; ainsi se trouvent constituées des ankyloses osseuses avec des modifications importantes des rapports des épiphyses.

† Il est même un type très particulier où le processus ankylosant est extensif, les articulations sacro-iliaques sont même atteintes mais il n'existe dans ces cas ni stade I et II des altérations sacro-iliaques de la classification de Forestier et Metzger (1939) ni ponts osseux juxta-discaux. Nous reprendrons sa description dans un prochain travail.

‡ Les très rares cas de lyse que nous avons noté daus des cas de spondylarthrite au niveau du poignet ou de la hanche ou de malacie (colonne cervicale) sont survenus chez des sujets de plus de 50 ans.

(1) *La goutte polyarticulaire*, qui est le diagnostic le plus difficile à éliminer; en effet, dans la goutte comme dans la polyarthrite, la localisation de début est souvent les pieds et les chevilles. Mais certains signes cliniques doivent permettre d'envisager le diagnostic de goutte: début et terminaison brutale de l'accès, localisation aux gros orteils. Par contre, une atteinte précoce d'un poignet ou d'une coude, exceptionnelle dans la goutte, oriente vers la polyarthrite. L'examen clinique doit comprendre la recherche des tophi sur les pavillons auriculaires, et des hygromas aux coudes. La radiographie peut révéler soit d'importantes géodes sous-corticales de la goutte, soit de petites géodes que l'on ne peut distinguer de celles de la polyarthrite. C'est bien souvent le dosage de l'acide urique sanguin qui confirmera ou infirmera le diagnostic de goutte.

(2) *La spondylarthrite ankylosante* à début par localisation au niveau des membres: l'examen radiologique systèmatique des articulations sacro-iliaques doit être fait. Nous n'avons voulu retenir pour notre étude que les sujets ayant un dossier radiologique suffisant et une uricémie.

Conclusions

Il nous semble se dégager de l'étude de 48 dossiers cliniques et radiologiques de polyarthrite masculine quelques notions:

(1) L'âge joue un rôle dans le type d'altérations radiologiques avancées; images d'ankylose osseuse chez le jeune du même type que celles que l'on rencontre dans la spondylarthrite; images de destruction ou d'atrophie osseuse, associées ou non à des condensations, chez le sujet de plus de 30 ans.

(2) L'élément articulaire inflammatoire nous paraît variable aussi suivant l'âge: gonflement plus ou moins dur, sorte de blindage chez le jeune; proliférations synoviales chez le sujet de plus de 30 ans; douleurs simples chez le vieillard. L'épanchement plus ou moins abondant est surtout noté chez l'adulte de plus de 30 ans et ce n'est que chez lui que l'on rencontre les petits épanchements multiples réalisant la forme hydrarthrodiale.

(3) Il semble exister une relation entre l'élément inflammatoire et l'altération radiologique qui apparaît lors de la persistance de l'élément inflammatoire; la prolifération s'accompagne alors de destruction, l'épanchement d'une ostéoporose, l'épaississement dur ou blindage, d'ankylose osseuse.

Ce travail est basé sur un petit nombre de cas et il devrait être confirmé par un travail plus important, mais il nous a paru intéressant de mettre déjà en évidence l'importance de la notion d'âge; le terrain joue donc un rôle.

L'étude des altérations radiologiques suivant l'âge devra être faite chez la femme; mais dès maintenant nous pouvons dire que les phénomènes d'ankylose, sans destructions osseuses, n'apparaissent que chez l'adolescente ou la jeune adulte. Notre documentation ne nous permet pas de dire si les phénomènes destructifs ou atrophiques n'apparaissent uniquement qu'à partir de l'âge de 30 ans.

De plus il est necessaire d'avoir des clichés radiographiques de toutes les articulations aux divers stades de leur évolution car, comme nous y avons fait allusion plus haut, les altérations diffèrent suivant les localisations.

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Rheumatoid Arthritis in the Male

SUMMARY

Records of 48 male patients with rheumatoid arthritis were investigated. They comprised only cases where full clinical and radiological data, including *x* rays of the sacro-iliac joints (to exclude ankylosing spondylitis) and of at least one affected joint, were available. The duration of the disease varied from a few months to 45 years. In nine cases the patients were followed-up for long periods, a few of them for over 15 years.

Incidence.—The proportion in the male is given as 20 per cent., but only polyarticular symmetrical arthritis was considered.

Antecedents.—A precipitating factor, such as focal infection, articular trauma, fracture of the skull, and cerebral stroke, was elicited in eleven cases.

Age of Onset.—In five cases the disease began between the ages of 16-20, in 28 cases between 30-50, and in one case after the age of 70.

Early Symptoms

(*i*) *Local.*—A monarticular onset was seen in six cases, this single localization persisting for periods ranging from a few months to 6 years. In thirty cases with onset in two to four joints only, progress towards a typical symmetrical polyarthritis was slow (31 years in one case). Initial polyarthritis was seen in ten cases, in half of which the manifestations were intermittent.

(*ii*) *General.*—The high incidence of general symptoms in the male is stressed. In 32 cases out of 48 the onset was marked by fever, loss of weight, or both.

Clinical and Radiological Changes

This section is primarily concerned with clinical and radiological changes in the wrist joint. In the light of the observed relationship between morbid manifestations and the age of the patient, the material has been classified as follows:

(*a*) *Ankylosis in the young adult without bone destruction.* This form was seen in six patients aged 18-26 years. Clinically there was stiffness and sometimes locking of the joints, muscular atrophy masked by a hard thickening of the skin, which was pale and cold, and induration of the finger joints, but little deformity. *X* rays showed ankylosis without destruction or structural changes.

(*b*) *Proliferation and destruction in subjects over 30.*—Thirty cases (mostly between the ages of *40-50*) exhibited the typical proliferative, destructive, and atrophic manifestations of established rheumatoid arthritis. It is stressed that such manifestations were observed also in cases of 2-3 years' duration only, contrasting with the non-destructive changes in the young adult.

(*c*) *Effusion usually in the age group* 40-50.—Here synovial effusions dominated the picture, while other symptoms such as osteoporosis, deformity, pain, and functional impairment were either absent or slight.

(*d*) *Painful polyarthritis in subjects over 70.*—In two elderly patients, the joints—mainly hip and shoulder—were extremely painful and tender, and there was fever and loss of weight. No radiological changes were observed.

Other Clinical Observations

Adenopathy was noted in eight cases. Nodules were seen in nine cases; they seemed to be more frequent in men than in women. Dupuytren's contracture existed in two cases.

Of particular interest were marked trophic changes of the skin, often simulating scleroderma; these were seen in seven patients, three of them young. Thinning of the skin, frequently seen in female arthritis, was not found in this series.

Polyarthritis in the male is a severe and painful affection; seven cases were bedridden, and in 31 functional impairment made regular work impossible; among the latter were two young men with extensive ankylosis. Furthermore, rheumatoid arthritis in the male is less responsive to treatment.

Differential Diagnosis

At the mono-arthritic stage the possibility of scapular peri-arthritis and of infectious, particularly tuberculous, arthritis should be considered.

In cases of oligo-arthritis the absence of tophi and of uricaemia will exclude gout. To avoid confusion with ankylosing spondylitis commencing in the limbs, an *x* ray of the sacro-iliac joints is necessary.

Conclusions

The authors stress the importance of age as a factor determining the type of lesions: ankylosis in the young, synovial proliferation and bone destruction in the over-30s, pain in the old. The over-30 age group is more prone to suffer from synovial effusion and they alone may be subject to small multiple effusions. The relationship between the inflammatory elements and the radiological changes should be noted: proliferation is accompanied by destruction, effusion by osteoporosis, and hard thickening by bony ankylosis.

Poliartritis masculina

CONCLUSIONES

Del estudio de los datos clínicos y radiológicos de 48 casos de poliartritis masculina parecen emanar algunas nociones:

(1) La edad juega un papel en el tipo de alteraciones radiológicas avanzadas; imágenes de anquilosis ósea en el joven del mismo tipo que las que se encuentra en la espondilartritis; imágenes de destrucción o de atrofia ósea, a veces asociadas con condensaciones, en el sujeto de más de 30 años.

(2) El elemento articular inflamatorio también nos parece variable según la edad: tumefacción más o menos dura, especie de coraza, en el joven; proliferaciones sinoviales en el sujeto de más de 30 años; dolores simples en el viejo. El derrame más o menos abundante se nota en el adulto de más de 30 años y en él sólo se encuentra los pequeños derrames multiples que realizan la forma hidartrodial.

(3) Parece que existe una relación entre el elemento inflamatorio y la alteración radiológica que sobreviene al persistir el elemento inflamatorio; la proliferación acompáñase entonces de destrucción, el derrame de una osteoporosis, endurecimiento o coraza de anquilosis ósea.

Este trabajo se basa en un pequeño número de casos y precisa confirmación por un trabajo más importante, pero nos parece interesante exponer ahora la importancia de la noción de edad; el terreno juega pues uñ papel.

CLINICAL INVESTIGATION OF THE VALUE OF SYNTHETIC HYALURONIDASE INHIBITORS IN RHEUMATOID ARTHRITIS

BY

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The possible role of hyaluronidase in the pathogenesis of rheumatic diseases was first suggested some ten years ago (Wallenfels, 1941; Hahn, 1944), since which time the subject has received a fair amount of attention. Certain observations in the literature suggest some interrelationship between the pathological changes of the mesenchymal tissue and an imbalance of the hyaluronidase-hyaluronic acid system. In rheumatoid arthritis the viscosity of the joint exudate is lower than that of synovia in normal subjects (Robertson and others, 1940). The degree of polymerization of the hyaluronic acid in such exudate is likewise lowered (Ropes and others, 1947). It has also been shown that in rheumatoid arthritis the viscosity of the joint exudate can be increased by intra-articular injection of cortisone (Bauer, 1950; Ekman and others, 1952). The *in vitro* inhibitory action of the exudate on hyaluronidase is also appreciably enhanced after such an injection (Ekman and others, 1952).

While studying various substances for their effect on the enzymatic breakdown of hyaluronic acid, it was found that certain polycondensed diphenylmethane and triphenylmethane derivatives possess the power strongly to inhibit such hydrolysis *in vitro* (Hahn, 1952). Some of these substances were also tried in animal experiments and proved to be also strong inhibitors of hyaluronidase *in vivo* (Fabinyi-Szebehely and others, 1952).

The purpose of the present investigation was to find whether these substances might be of any value in the treatment of rheumatoid arthritis.

Synthetic Hyaluronidase Inhibitors (SHI) Tested

(1) *Compound 21 P* (Polycondensed hexahydroxy-tricarboxy-triphenyl-methane). This substance is the product of simultaneous oxidation of polycondensed tetrahydroxy-dicarboxy diphenylmethane and dihydroxy benzoic acid. Its inhibitory power *in vitro* is 2,490 relative units (resorcinol = 1). It is the most active hyaluronidase inhibitor both *in vitro* and *in vivo* hitherto described. Its oral LD50 is > 20 mg./g. in mice.

(2) *Compound 7 P* (Polycondensated tetrahydroxy-dicarboxy diphenyl-methane). This compound is the product of condensation of dihydroxy benzoic acid with formaldehyde under conditions favouring the formation of molecules of fairly large size. It possesses less inhibitory power than Compound 21 P. Its oral LD50 is 10 mg./g. in mice.

(3) *Compound 16 P* (Polycondensed hepta-hydroxy-tricarboxy triphenyl-methane). This compound was derived from polycondensed methylene-di-β-resorcylic acid by substitution with 2.3.4-trihydroxy-6-carboxy phenyl radicals in the methylene groups. The inhibitory power of this substance is slightly less than that of Compound 7 P *in vitro*, but approximately the same *in vivo*. Its oral LD50 is 5·4 mg./g. in mice.

Material

The material consisted of 101 cases (36 males and 65 females) with rheumatoid arthritis treated in this Department. Of these, 85 were in-patients and sixteen out-patients. The ages ranged from 7 to 62 years (average 42). At the commencement of the trial the patients had had rheumatoid arthritis for 1 to 27 years (average 8) and had been suffering from an exacerbation for 2 to 72 months (average 12). All of them showed pronounced symptoms and signs of the disease which was in an active stage. The in-patients were receiving selective physiotherapy and 34 of them were being treated with gold compounds. Most of them were receiving salicylate. This treatment was stopped immediately before or soon after the commencement of the trial. As to the out-patients, all previous medication was suspended for the duration of the trial, but no changes in regimen were prescribed. At the beginning of the trial no tendency to abatement was demonstrable in any of the patients.

Method

The following joint symptoms were recorded: resting pain, pain on movement, pain on weight-bearing, and tenderness to palpation. Four degrees of intensity (0, 1, 2, 3) were distinguished.

The joint signs, peri-articular swelling, capsular swelling, exudate, and impaired range of motion, were evaluated by two of us (S.T. and E.T.) together. For purposes of control, a number of cases were examined by each of us separately and our records were in good agreement. We distinguished five degrees of peri-articular swelling (0, 1, 2, 3, 4), three degrees of capsular swelling (0, 1, 2), four degrees of exudate (0, 1, 2, 3), and two degrees (fair, good) of improvement in range of motion, as measured by a protractor.

Altogether 1,490 joints were examined in this way on the average four to five times. This total was made up as follows:

cervical vertebrae, 4;	proximal interphalangeal joints, 360;
shoulders, 18;	knees, 146;
elbows, 42;	ankles, 82;
wrists, 126;	metatarso-phalangeal joints, 190;
metacarpo-phalangeal joints, 520;	

lumbar vertebrae, 2.

In the evaluation of the effect of the compounds all of the joints studied in any one patient were taken as a single joint. For each symptom and sign the averages of the values recorded for the individual joints were calculated at every examination. The values for metacarpo-phalangeal joints, proximal interphalangeal joints and metatarso-phalangeal joints included in the above calculation were averages of the recordings made for the five joints of the hand or foot in question.

Any difference found between the averages of the initial recordings and the averages of the final recordings was calculated as a percentage of the initial values. Decreases by 1 to 25 per cent., 26 to 50 per cent., 51 to 75 per cent. and 76 to 100 per cent. are given in the Tables as +, ++, +++, and ++++.

The following laboratory tests were carried out: Heller's test, Almén's test, urinary sediment, erythrocyte sedimentation rate, percentage of haemoglobin, counts of erythrocytes, leucocytes, eosinophilic leucocytes, and thrombocytes, differential blood count, and prothrombin index. Temperature charts were also plotted.

The substances were administered *per os* in 0·5-g. tablets three to six times daily. The largest dose given was 2 g. The total daily dose varied from 3 to 10 g.

Two inhibitors were sometimes tried in immediate succession in the same patient.

Results

(1) *Compound 21 P.*—Fifty subjects (39 in-patients and 11 out-patients) received Compound 21 P daily for 3 to 111 days (average 41). In order to obtain an idea of the optimal dosage, the daily dose was varied from 4·5 to 10 g. (average 7·0). Five doses of 1·5 g. daily were found to be suitable for adults. The total amount received by a single patient varied between 23 and 738 g. (average 284).

Altogether 751 joints were regularly studied in these fifty patients.*

In all patients the clinical effect produced was favourable. In one case the administration of the substance was interrupted after 3 days. Already within this time the regression of the pronounced symptoms and signs of the joints recorded was striking. The abatement of the joint symptoms and signs is apparent from Table I. In 36 patients in whom the initial abatement of the symptoms could be dated with certainty, it occurred within 5 days on the average. The regression of the signs was usually demonstrable within 7 days. The rate of improvement of the peri-articular swelling was usually highest during the first 2 to 3 weeks of the SHI administration.

As seen from Table I, in most of the cases no pronounced reduction of the capsular swelling was obtained. We have shown that streptochinase in combination with streptodornase, when injected intra-articularly, breaks down any fibrin clots in the joints. This disintegration of the fibrin clots and aspiration of the joint exudate reduces capsular swelling to such an extent that the capsule appears practically normal on palpation. Therefore in some

* Since the preparation of this paper for the press another ten out-patients have received similar doses with equally good results.

TABLE I

CLINICAL INVESTIGATION OF COMPOUND 21 P (50 SUBJECTS)

	Symptoms	No. of Cases						
		Initially without Symptoms	Improvement					Symptoms not Recorded
			0	+	++	+++	++++	
Subjective	Resting pain	27	2	—	2	3	16	—
	Pain on movement	2	4	1	9	11	22	1
	Pain on weight-bearing	7	5	—	1	14	12	11
	Tenderness to palpation	8	6	1	7	6	18	4
Objective	Peri-articular swelling	—	—	3	17	15	14	1
	Capsular swelling	2	28	1	1	12	1	5
	Exudate	11	4	3	7	5	9	11

patients "capsular swelling" may be ascribed to a deposition of fibrin in the joints.

Of 43 patients with limited movement of the joints, a fair improvement in the range of motion was noted in 31 and a good improvement in five.

In eight of twelve patients, low grade fever passed off. Heller's test and Almén's test was regularly negative in all the fifty patients, and the urinary sediment, which was examined on various occasions, was always normal. This compound had no effect on the percentage of haemoglobin or on the number of erythrocytes. The E.S.R. was followed in 47 cases, in 45 of which it was increased from the beginning. A moderate decrease was observed in sixteen cases, in two of which the level returned to normal. In seven a moderate increase in E.S.R. was recorded, and in 24 no appreciable change was observed. Transient leucocytosis was noted in two of forty cases. In five of 34 patients a moderate transient increase in the total number of eosinophilic leucocytes was noted (examined *ad modum* RUD). These five patients had not received gold therapy. Neither the total number of thrombocytes nor the prothrombin index were affected. No appreciable change in body weight was noted.

The clinical improvement was often accompanied by a usually transient sensation of warmth, flushes, and sometimes sweating, particularly among the females. Occasional looseness of stools soon passed off without any special treatment, but in two cases it was necessary to decrease the daily dose from initially 7·5 to 6 g. No other side-effects were observed.

Compound 7 P.—28 subjects (23 in-patients, 5 out-patients) received 3 to 9 g. (average 6) of Compound 7 P daily for 3 to 98 days (average 29). The total amount received by a single patient varied between 18 and 732 g. (average 178).

Altogether 423 joints were regularly studied. The effect was similar to that produced by Compound 21 P but was less pronounced (Table II). In the case in which the substance was administered for only 3 days the clinical effect was obvious. In five cases no improvement was recorded.

No side-effects were observed.

Compound 16 P.—23 subjects, all in-patients, received 3 to 9 g. (average 7) of Compound 16 P daily for 5 to 56 days (average 21). The total amount received by a single patient varied between 33 and 336 g. (average 137).

Altogether 316 joints were regularly studied. The effect was similar to that produced by Compound 21 P but less pronounced (Table III). Improvement was recorded in every patient treated with this substance.

TABLE II

CLINICAL INVESTIGATION OF COMPOUND 7 P (28 SUBJECTS)

Symptoms		No. of Cases						
		Initially without Symptoms	Improvement					Symptoms not Recorded
			0	+	++	+++	++++	
Subjective	Resting pain	6	5	—	1	4	11	1
	Pain on movement	—	7	—	3	10	6	2
	Pain on weight-bearing	1	7	—	9	—	7	4
	Tenderness to palpation	4	6	—	3	1	3	11
Objective	Peri-articular swelling	—	6	5	6	7	2	2
	Capsular swelling	—	18	—	—	—	—	10
	Exudate	6	4	3	4	3	—	8

TABLE III

CLINICAL INVESTIGATION OF COMPOUND 16 P (23 SUBJECTS)

Symptoms		No. of Cases						
		Initially without Symptoms	Improvement					Symptoms not Recorded
			0	+	++	+++	++++	
Subjective	Resting pain	13	—	—	—	2	7	1
	Pain on movement	1	7	—	1	6	5	3
	Pain on weight-bearing	5	5	—	—	2	7	4
	Tenderness to palpation	4	3	—	1	3	1	11
Objective	Peri-articular swelling	1	5	2	6	7	2	—
	Capsular swelling	1	14	—	1	—	—	7
	Exudate	2	4	—	5	3	5	4

Effective doses sometimes caused severe diarrhoea that made it necessary to stop the administration of the substance.

Discussion

The material was selected in such a manner that spontaneous improvement could be excluded with reasonable certainty at the commencement of the trial. These requirements probably best fulfilled by long-standing cases, in patients suffering from a fairly long exacerbation. In our series the patients had had rheumatoid arthritis for 8 years on the average and had been suffering from an exacerbation for about 12 months.

In order to facilitate the evaluation of any differences in the condition of the joints we selected only those with striking changes, particularly with marked peri-articular swelling.

Rheumatoid arthritis often responds favourably to ordinary hospital regimen, and the initial signs of improvement usually appear within a few weeks. In our series, however, definite improvement was generally already recorded within 7 days.

Of the patients who received Compound 21 P, sixteen were also treated simultaneously with gold compounds. No difference was observed between the clinical results obtained in the patients receiving gold compounds and those in the rest of the group.

Compounds 21 P and 7 P were tried on both in-patients and out-patients and produced equally good results in both. Compound 16 P was not administered to out-patients. The out-patients received no other kind of therapy and no changes in regimen were prescribed.

Suspension of salicylate administration at the start of the trial was usually followed by a transient increase in the joint pain. This is because the compounds tested have practically no analgesic effect. The subsequent marked decrease in the severity of the joint symptoms recorded after a few days' administration of the compounds must be interpreted as an improvement in the condition of the joint. This gave fairly accurate information about the onset of the effect of the compounds tested on the joint symptoms. Salicylate was a source of comfort to most of the patients. A few days after this drug was replaced by the SHI the joints became less painful than they had been during the previous salicylate administration. Although the patients themselves also noticed a decrease in the swelling of the joints, they did not feel quite satisfied. It is suggested that this may be ascribed to some euphoric effect possessed by salicylate but not by the substances tried.

Observations made in the present investigation suggested the following conclusions:

(1) Compound 21 P produces the most favourable clinical results and practically no side-effects.

(2) Compound 7 P is the least effective clinically and is accompanied by practically no side-effects.

(3) Compound 16 P when given in effective therapeutic doses produces severe diarrhoea.

It is, of course, too early to say whether the results obtained will last for any length of time without further medication or whether improvement will continue. Further investigations are in progress.

Summary

Three synthetic hyaluronidase inhibitors:

polycondensed hexahydroxy-tricarboxy-triphenylmethane (Compound 21 P)

polycondensed tetrahydroxy-dicarboxy-diphenylmethane (Compound 7 P)

polycondensed heptahydroxy-tricarboxy-triphenylmethane (Compound 16 P)

were investigated for their clinical value in rheumatoid arthritis.

The material consisted of 101 cases of active rheumatoid arthritis (85 in-patients, 16 out-patients). Symptoms and signs in altogether 1,490 joints were recorded four to five times during the trial. All three compounds had similar pronounced beneficial effects on the joint symptoms and signs.

Compound 21 P, which proved to be the strongest hyaluronidase inhibitor *in vitro* and *in vivo*, produced the strongest clinical reaction and was attended by practically no side-effects.

Our thanks are due to Dr. Gunnar Edström for numerous facilities put at our disposal.

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Recherches cliniques sur la valeur des inhibiteurs synthétiques de la hyaluronidase dans l'arthrite rhumatismale

RÉSUMÉ

On étudia, du point de vue de leur valeur clinique dans l'arthrite rhumatismale, les trois suivants inhibiteurs synthétiques de la hyaluronidase;

hexahydroxy-tricarboxy-triphénylméthane polycondensé (Composé 21 P),

tetrahydroxy-dicarboxy-diphénylméthane polycondensé (Composé 7 P),

heptahydroxy-tricarboxy-triphénylméthane polycondensé (Composé 16 P).

Le matériel consistait en 101 cas d'arthrite rhumatismale active (85 malades hospitalisés et 16 externes). Au cours des recherches on prit note à quatre ou cinq reprises de signes et de symptômes dans 1.490 articulations. L'effet sur les signes et symptômes articulaires fut favorable et similaire pour les trois composés.

Le Composé 21 P, qui s'avéra l'inhibiteur le plus fort de la hyaluronidase *in vitro* et *in vivo*, donna aussi la plus forte réaction clinique, sans virtuellement s'accompagner d'effets secondaires.

Investigación clínica sobre el valor de los inhibidores sintéticos de la hialuronidase en la artritis reumatoide

SUMARIO

Los tres siguientes inhibidores sintéticos de la hialuronidase fueron estudiados para determinar su valor en la artritis reumatoide:

hexahidroxi-tricarboxi-trifenilmetano policondensado (Compuesto 21 P),

tetrahidroxi-dicarboxi-difenilmetano policondensado (Compuesto 7 P),

heptahidroxi-tricarboxi-trifenilmetano policondensado (Compuesto 16 P).

El material consistió de 101 casos de artritis reumatoide activa (85 enfermos hospitalizados y 16 externos). Durante la investigación se tomó nota cuatro o cinco veces de los signos y síntomas en un total de 1,490 articulaciones. Los tres compuestos ejercieron un efecto similar y muy favorable sobre los signos y síntomas.

El Compuesto 21 P, que se mostró el inhibidor más fuerte de la hialuronidase *in vitro* e *in vivo*, produjo también la más fuerte reacción clínica sin virtualmente dar lugar a efectos secundarios.

VALUE OF INTRA-ARTICULAR INJECTIONS IN OSTEO-ARTHRITIS

A CONTROLLED SERIES

BY

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In view of the controversial reports on the value of intra-articular injections in the treatment of osteo-arthritic conditions it was decided to carry out a clinical experiment under strict control to investigate this problem.

For that purpose groups of cases suffering from osteo-arthritis of the hip and knee were treated by intra-articular injections using different types of solutions at different *p*Hs, and the results obtained were compared with those in a control group.

Waugh (1938) was the first to treat arthritic joints by the intra-articular injection of a stable solution of procaine lactic acid at *p*H 5·0. He based this treatment on previous observations that synovial fluid of arthritic joints was consistently alkaline, and on the observations of Starling (1932) that the hydrogen ion concentration in a haematoma around a fracture was strongly acid in reaction. This acid shift was a physiological mechanism for the solution of bone calcium and for tissue regeneration. Waugh (1936) suggested that the acidity possibly acted as a stimulus to polymorphonuclear leucocytosis and later to local mesoblastic proliferation. This assumption was also based on his work on the *p*H values of purulent discharges in cases of osteomyelitis and compound fractures. He found that the normal *p*H of synovial fluid of joints was around 7·4. Twenty-four hours after an injury the *p*H became acid, and it returned to normal or slightly to the alkaline side of neutrality within 7 days. He assumed that the acid, identified as sarcolactic acid, was derived from local cell tissue damage and degeneration. On the above observations he stipulated that the joint acidity was a physiological response to trauma designed to excite local leucocytosis and repair. Procaine lactic acid intra-articular injections were therefore used in an endeavour to imitate this physiological reaction.

Nicholson (1948) strongly criticized these views on the ground that Waugh's experimental observations were limited in number and that the methods used for estimating the *p*H values were crude. Estimation of the *p*H of body fluid could only be measured accurately *in vivo*.

Coste and Morin (1939) tried different solutions in the treatment of 24 cases of osteo-arthritis of the hip joint and reported equivocal results with a concentrated solution of procaine. Various other solutions have also been tried: Fletcher (1943) reported very good results with lipiodol and gomenol injections. Of twenty cases thus treated thirteen (65 per cent.) became symptom-free and maintained the improvement at the end of 3 years; two other cases were also improved.

Crowe (1944), using a 1 per cent. solution of acid potassium phosphate, treated 284 painful and swollen rheumatic joints and reported recovery of full function and complete disappearance of pain in 68 cases (24 per cent.). In 102 cases (36 per cent.) deformity and swelling were reduced and range of movement increased. In 114 cases (40 per cent.) only temporary subjective alleviation of symptoms was experienced. The best results were obtained in quiescent cases with a normal E.S.R. Usually one injection sufficed to produce the improvement.

Baker and Chayen (1948), in an attempt to compare the effects of procaine lactic acid solution and a neutral solution of procaine in isotonic saline, obtained equally satisfactory results with both solutions. They attributed the benefit to the psychological effect of the prompt relief of pain by the procaine in conjunction with the lubricating action of the fluid injected. There was a tendency to recurrence of symptoms a fortnight after the injection. R. Kron (1948) reported encouraging results with an isotonic solution of sodium bicarbonate.

Lawther (1949), using solutions of procaine lactic acid and 2 per cent. procaine hydrochloride in the treatment of degenerative disease of the hip, reported equally satisfactory results in both series. The relief of pain was more marked than the increase in range of movement.

Waugh (1945) reported his further experience of the treatment of over 1,200 cases of different types of arthritic joints by the intra-articular injection of procaine lactic acid. Though he gave no statistical analysis of his results, he estimated that 70 per cent. of cases were rendered free from pain with sufficient restoration of function to allow them to return to their normal occupation.

Mawson (1946) and Heald and Martin (1947) also reported encouraging results in cases of mixed arthritis treated by the Waugh method.

The majority of reports in the literature have been concerned with the effects of intra-articular injections of the hip joints; in this joint, for anatomical reasons, it is not easy to be certain that the injection is truly intra-articular.

Dobson (1948), checking the anatomical accuracy of intra-articular injections of the hip in cadavers, used a solution of carmine in glycerine and found at dissection that 65 per cent. of the injections were successful. In a second series she obtained a 67 per cent. success and recommended the anterior approach as giving slightly better results (Dobson, 1952).

Many theories have been put forward in an attempt to explain the reported relief of symptoms following various intra-articular injections. Tarsy (1938) suggested that the effects of procaine lactic acid were due to the anaesthetic and analgesic properties of the procaine, which acts by interrupting the vicious circle of pain, spasm and congestion. Waugh (1938), on entirely empirical evidence, concluded that the swing of the alkaline *p*H of the joint to the acid side stimulated local leucocytosis and repair by mesoblastic proliferation.

Sacks (1949) attempted to explain the mechanism of relief of symptoms on physical and biochemical grounds. In articular cartilage, chondroitin sulphate is combined with protein to form a glycoprotein. Chondroitin sulphate can be extracted from this protein linkage by dilute alkali, the molecule being easily depolymerized or broken down. The molecule is therefore extremely sensitive to the *p*H of the surrounding fluid, and it is this factor which is of fundamental importance in cartilage physiology. Since all acid substances would tend to reduce depolymerization of chondroitin sulphate in the cartilage matrix, the relative value of acid substances alone or in combination with procaine becomes obvious.

The origin of joint pain has for long been a controversial subject. The anatomy of the innervation of the knee and hip joint has been well demonstrated by Gardner (1948). This knowledge was applied by Fell (1952) to show on human volunteers that localized referred pain from the hip corresponded to the anatomical pattern of the innervations of the joint capsule. On the assumption that pain in arthritic joints arises largely from fibrosis of the capsule, the regions corresponding to the localized referred pain were injected with procaine, with good results but temporary relief. Kellgren (1950), investigating the pain pattern of the knee joint, found that the fibrous capsule and its ligaments played an important role in articular sensation and appeared to be the major source of joint pain. The synovial membrane was poorly supplied with pain end-organs but was rich in autonomic nerve fibres.

Methods

In an attempt to find an answer to some of the problems referred to above, especially the part played by the *p*H of the solutions injected into joints of cases suffering from osteo-arthritis of the hip or knee, joints were allocated to four different treatment groups by random sampling. The joints were treated with solutions of

(*i*) lactic acid at a *p*H of approximately 5·4,
(*ii*) 2 per cent. alkaline procaine at a *p*H of 7·4,
(*iii*) normal saline buffered to a *p*H of 7·2.

In addition a control group was included in which the joints were penetrated by the needle but no fluid injected. All cases received physiotherapy as indicated. The course of treatment consisted of a total of six injections each of 10 ml. given twice-weekly for 3 weeks. In the case of the hip the anterior approach was invariably used; for the knee joint the antero-lateral approach either below or above the patella was commonly chosen. When either of these latter was technically difficult the medial mid-patella route was used. None of these techniques was found to be unduly difficult or unpleasant to the patient.

The clinical condition of the joint was assessed before each injection, at the end of treatment, and 3 months and 6 months after completion of treatment.

The main criteria used in the assessments were the change in the degree of pain as reported by the patient and the change in range of movement of the joint. Swelling, tenderness, and any improvement of function were also noted.

The clinical change in pain and movement after treatment was recorded as "no change", "slight improvement", or "marked improvement". An increase in range of movement of 10-20° was considered as "slight improvement", and an increase in range of 20° or above as "marked improvement". As the range of movement in the majority of the knees at the onset of treatment was full, only the change in mobility which occurred in the hips could be analysed. All assessments were made by the same observer using the same criteria of improvement throughout.

In cases with small effusion, only sufficient fluid required for laboratory examination was aspirated. In a few cases with a large effusion the *p*H of the fluid was examined before injecting 10 ml. lactic acid, and then again at 2-, 4-, and 10-minute intervals, and in some

cases again at the end of 3 and 7 days. All *p*H estimations were carried out almost immediately after aspiration in a room adjoining the theatre. The *p*H values in the last four cases were examined at first by the Comparator method, but they were estimated by a *p*H meter.

In the present series the effects of intra-articular injections were studied in 189 osteo-arthritic joints (108 hips and 81 knees).

Results

Pain.—There was a tendency to improvement as judged by pain during the period of treatment in all groups, including the controls. At completion of treatment there was little difference in the number of improved in each group. After 3 months the knees treated with lactic acid or procaine, and the hips treated with procaine showed slightly better results than the other groups (Table I). The fact that the procaine-treated hips progressed better than those injected with lactic acid might be explained by the procaine having had a direct analgesic effect on the capsule through part of the injection being extra-articular.

On statistical evaluation, however, using the four-fold χ^2 test, it becomes obvious that the above impressions of the effect of intra-articular injections on pain may have been due to chance and are not proven (Table I).

Movement.—On examining the effect of treatment on movement, there appeared to be some increase in range in the groups injected with lactic acid, procaine, or saline as compared with the controls. In other words the use of any fluid may sometimes assist in the promotion of movement in the hip (Table II).

TABLE I

CHANGE IN DEGREE OF PAIN IN KNEES AND HIPS

Joints	Treatment	No. of Joints Treated	Change in Degree of Pain									*p* Value 3 Months after Treatment
			After 3 Injections			After 6 Injections			3 months after Treatment			6 months after treatment
			No change	Slight Improvement	Marked Improvement	No Change	Slight Improvement	Marked Improvement	No Change	Slight Improvement	Marked Improvement	Improvement Maintained	
Hips	Lactic Acid	28	22	6	0	14	12	2	18	8	2	5	$0{\cdot}90>p>0{\cdot}80$
	Alkaline Procaine	29	21	7	1	12	13	4	13	13	3	13	$0{\cdot}30>p>0{\cdot}20$
	Saline	25	20	4	1	12	12	1	18	7	0	6	$0{\cdot}50>p>0{\cdot}30$
	Needle Prick	26	17	9	0	10	14	2	17	8	1	8	—
Knees	Lactic Acid	23	15	8	0	8	12	3	8	11	4	11	$0{\cdot}50>p>0{\cdot}30$
	Alkaline Procaine	19	17	2	0	7	9	3	6	9	4	13	$0{\cdot}70>p>0{\cdot}50$
	Saline	21	17	4	0	12	7	2	13	6	2	7	$0{\cdot}50>p>0{\cdot}30$
	Needle Prick	18	12	5	1	7	7	4	10	6	2	5	—

TABLE II

CHANGES IN RANGE OF MOVEMENT OF HIPS

Treatment	No. of Joints Treated	Change in Range of Movement (hips only)								
		After 3 Injections			After 6 Injections			3 Months after Treatment		
		No Change	Slight Increase	Marked Increase	No Change	Slight Increase	Marked Increase	No Change	Slight Increase	Marked Increase
Lactic Acid	26	22	4	0	18	7	1	20	6	0
Alkaline Procaine ..	27	24	3	0	17	10	0	19	7	1
Saline	24	20	4	0	17	6	1	18	5	1
Needle Prick	25	24	1	0	21	3	1	20	4	1

TABLE III

*p*H VALUES OF SYNOVIAL FLUID OF KNEE JOINTS BEFORE AND AFTER 10 ml. LACTIC ACID INJECTED INTRA-ARTICULARLY

Diagnosis	Case No.	*p*H Values					
		Before Injection	2 Minutes After	4 Minutes After	10 Minutes After	3 Days After	7 Days After
Osteo-arthritis	79	7·6	7·5	7·4	—	7·6	—
Osteo-arthritis	66	7·5	—	7·5	—	7·5	7·5
Osteo-arthritis	95	7·4	7·4	6·8	—	—	—
Osteo-arthritis	77	7·6	7·4	7·4	—	—	—
Osteo-arthritis	62	—	—	—	—	7·5	—
Osteo-arthritis	147	7·5	—	—	—	7·5	—
Osteo-arthritis	87	7·5	—	—	—	—	—
Osteo-arthritis	164	*7·35	*7·45	*7·48	*7·50	—	—
Osteo-arthritis	180	*7·46	*7·34	*7·23	*7·30	—	*7·40
Osteo-arthritis	181	*7·35	*7·30	*7·28	*7·28	—	*7·35
Osteo-arthritis	182	*7·30	*7·25	*7·45	*7·30	—	*7·30
Rheumatoid Arthritis	88	7·40	—	—	—	—	—
Rheumatoid Arthritis	166	—	—	—	—	7·4	—
Rheumatoid Arthritis	95	7·40	—	—	—	7·40	7·40

* *p*H values estimated directly by a *p*H meter.

Effusion.—The degree of effusion was measured in thirty knee joints, before and 3 months after treatment. The injections appeared to have no appreciable effect when compared with the control group.

Discussion

The improvement in pain obtained in all groups, including the control group, immediately after treatment suggests the psychological effect on the patient of a new treatment. It seems that the use of intra-articular injections of lactic acid in the treatment of osteo-arthritis of the hip and knee is of less value than that of alkaline procaine. Any beneficial effects of alkaline procaine cannot be ascribed to the alkalinity of the solution, as a saline solution of approximately the same *p*H failed to produce any sustained improvement. The anaesthetic property of the drug is likely to be the mechanism whereby the pain is relieved.

The average *p*H value of the synovial fluid of the knees in ten cases before treatment was 7·45 (range 7·30 to 7·60) (Table III). Two minutes after an injection of 10 ml. lactic acid solution there was a very slight fall in the *p*H value of the fluids in all but two cases, the average being then 7·27. A slight fall in the *p*H was also noted after 4 and 10 minutes. The values after 3 and 7 days respectively were all normal.

In two cases, the effects of adding the solutions of lactic acid to synovial fluid *in vitro* in the dilution of 1 in 4 and 1 in 2 had no effect in changing the original *p*H value of the fluid. In each case the *p*H remained constant at 7·40.

The *p*H values obtained in cases of osteo-arthritis of the knee were all within the normal range and did not agree with the high values of 8·0 and 8·8 reported by Waugh (1938). The small changes in the *p*H values after the injection of 10 ml. lactic acid was not significant and was well within the range of experimental error. It is well appreciated that the *in vitro* methods used do not reflect the true *in vivo* *p*H values, but the strong buffer action of synovial fluid has been demonstrated by the failure of the lactic acid added to synovial fluid to alter the *p*H value in two cases at the low dilutions of 1 in 4 and 1 in 2. Synovial fluid, by virtue of its chemical composition and physical state, is a strong buffer, and it is not surprising that the injection of such a weak acid as lactic acid should fail to alter the *p*H of the joint fluid to any appreciable extent.

In conclusion it is considered that intra-articular injections in the treatment of osteo-arthritis are of very limited value and should be reserved for cases who have failed to respond to other forms of treatment. In such cases a simple local anaesthetic is probably the solution of choice.

Summary

A series of 189 osteo-arthritic joints was injected with alkaline procaine, lactic acid, or saline, or needled without injection.

Some cases in each group improved, but the

differences between those receiving lactic acid or procaine, and those used as controls were not statistically significant. There was a suggestion that in some cases procaine relieved pain, especially in the hip, and that the injection of any fluid might increase the range of hip movement.

The *p*H of the joint fluid was normal before treatment in ten cases, and no large or lasting change in *p*H followed the injection of lactic acid.

I wish to thank Dr. G. D. Kersley for suggesting this work and for his helpful criticism and assistance. Dr. Bradford Hill co-operated in organizing the statistical planning of the experiment. My thanks are also due to Mr. J. Bastow for supplying many of the cases and to Messrs. Brady and Martin Ltd. of Newcastle-upon-Tyne for their trouble in preparing the special alkaline procaine solution used in this trial.

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Valeur des injections intra-articulaires dans l'ostéoarthrite. Série contrôlée.

RÉSUMÉ

On a injecté dans 189 articulations ostéoarthritiques de la procaïne alcaline, de l'acide lactique, du sérum physiologique, et on a fait des piqûres sans rien injecter.

Il y a eu quelques améliorations dans chaque groupe, mais les différences entre ceux qui avaient reçu de l'acide lactique ou de la procaïne et les témoins furent insignifiantes du point de vue statistique. On est porté à croire que dans quelques cas la procaïne aurait procuré un allègement de la douleur, surtout à l'articulation sacro-iliaque, et que l'injection d'un liquide quelconque tendrait à augmenter l'étendue du mouvement de cette articulation.

Le *p*H du liquide synovial, normal dans dix cas avant le traitement, ne subit pas de modification appréciable ni durable après l'injection d'acide lactique.

Valor de inyecciones intra-articulares en la osteoartritis. Series controladas.

SUMARIO

En 189 articulaciones se inyectó procaina alcalina, ácido láctico y suero fisiológico, y se introdujo agujas sin inyectar.

Hubo algunas mejorías en cada grupo, pero las diferencias entre los que recibieron ácido láctico o procaina y los testigos no tuvieron significancia estadística. Hubo indicaciones de que en ciertos casos la procaina aliviara el dolor, especialmente en la cadera, y que una inyección de cualquier líquido pudiera aumentar la extensión del movimiento en la articulación de la cadera.

El *p*H del líquido sinovial, normal antes del tratamiento en diez casos, no sufrió alteración apreciable o durable después de la inyección de ácido láctico.

COLLAGENOUS PSEUDOTUMOURS OF THE HANDS

BY

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Soft-tissue tumours on the dorsum of the hand in an area between the level of the radiocarpal and metacarpo-phalangeal joints frequently present a diagnostic problem.

These " collagenous pseudotumours " seem to represent a separate entity. Cases with less swelling have been regarded as instances of rheumatoid tenosynovitis, but in fact these lesions differ pathologically from those of tenosynovitis. In the past they have not been adequately treated, and the only effective treatment that can be suggested at present is drastic surgical eradication.

Material

Six cases have been selected from a series of ten recently investigated. Particulars of the six patients are given in the Table.

Case 1, coloured female, aged 25, first seen July 7, 1945, had noted painful " masses " about the size of an egg on both hands for the past 2 years. These " masses " were extremely painful, especially on movement of the fingers. The clinical diagnosis was multiple tumefaction of both hands, possibly pigmented villonodular tenosynovitis.

TABLE

SUMMARY OF HISTORIES OF THE SIX PATIENTS WHOSE CASES ARE REPORTED

Case No.	Sex	Race	Age	Family History	Previous History	Present Illness				Remarks
						Symptoms		Operation		
						Date	Site of Swelling	Site	Tourniquet	
1	F	C	25	Mother living, has tuberculosis and cancer	—	1945	Both hands	Left hand	No	Recurred but patient refused further operation
2	F	W	29	None	1938 Arthritis of left middle finger 1942 Subdeltoid tumour (removed at operation) 1944 Arthritis of left knee (fusion operation)	1947	Both hands	Both hands (with 3-week interval)	Yes	No recurrence
3	F	C	20	—	1945 " Rheumatism " 1947 Contractures of finger joints	1948 1949	Left wrist, hand, and fingers Left hand	(1) Left hand and wrist (2) Left hand	No Yes	Recurred No recurrence
4	F	C	63	—	1945 Severe rheumatoid arthritis successfully treated	1947	Left hand	Left hand	Yes	No recurrence
5	M	W	29	—	—	1948 1949	Right hand Two on right hand and one on right ankle	(1) Right hand (2) Right hand	No Yes	Recurred; also on ankle No recurrence
6	F	C	30	None	1939 Miscarriage 1942 Hysterectomy	1950	Right wrist	Right wrist	Yes	Did not heal quickly. Tuberculosis of lung developed

Laboratory Findings.—Urine normal. Complete blood count normal. Blood sedimentation rate 35 mm./1 hr (Westergren). Tuberculin test positive. No sputum could be examined.

Operation.—Three tumours—one just over the styloid process of the ulna, one over the midportion of the fifth metacarpal, and one just between the two—were seen on the left hand. A 3-in. longitudinal incision was made over the dorsolateral aspect. Sharp and blunt dissection was carried out and much oozing was encountered. A soft, greyish, friable tumour mass surrounded the tendons of the common extensors of the fingers; the tendons were strangulated and atrophied, and the mass was so intensely adherent that it was impossible to remove all of it. After careful haemostasis and closure, an anterior moulded plaster-of-Paris splint was applied. The post-operative course was uneventful.

Pathologist's Report (Dr. H. L. Jaffe).—A number of fragments of thickened and congested tendon sheaths, were found on section to be hypertrophied, oedematous, and inflamed, and heavily infiltrated by lymphocytes, plasma cells, and macrophages, and in places by nests of polynuclear leucocytes. The inflamed tenosynovium was covered in places by fibrin exudate. This was described as "chronic but apparently still active tenosynovitis, possibly of rheumatoid origin".

Comment.—No tourniquet was used and this was one reason why the tumour could not be removed completely. It recurred in less than 5 months, was painful, and impaired tendon function. *X*-ray therapy (100r weekly) was given, but no improvement was noted for the next 6 months. The patient would not submit to another operation and was lost sight of.

Case 2, white female, aged 29, had been seen in 1942 when a large cystic mass containing more than 100 rice bodies, but with no evidence of tuberculosis, was removed from the right subdeltoid area. She was reported to have had arthritis of the right middle finger in 1938, with spontaneous recovery.

In 1944 she complained of increasing pain and limitation of motion in the left knee. She connected this with an automobile accident in 1941. At this time *x* rays showed changes characteristic of rheumatoid arthritis. Blood sedimentation rate 37 mm./1 hr (Westergren). Formogel reaction positive. At operation the left knee joint showed extensive destruction of all its cartilaginous constituents, and appearances characteristic of rheumatoid arthritis. A fusion operation was performed and recovery was uneventful.

In 1947 a soft mass had formed upon the dorsum of each hand, 1½ in. distally to the anatomic snuff box on the right, and more towards the centre of the dorsum of the wrist on the left. A fusiform swelling of the middle joint of both long fingers was noted. Active and passive motion of the metacarpal and proximal interphalangeal joints of the index and middle fingers was limited.

Laboratory Findings.—Sedimentation rate 39 mm./1 hr (Westergren). Blood count normal. Wassermann reaction negative.

Operation.

Right Hand: A greyish-red, almost rubbery, growth was tunnelled by and adherent to the tendons of the extensor pollicis longus and extensor carpi radialis brevis and longus in the right hand.

Left Hand: (3 weeks later) the tendons of the common extensor, indicis proprius, and digitus quintus proprius were found to be involved, some being half their usual size, though their power was not restricted.

In each case a pneumatic tourniquet was used and all the collagenous tissue removed by careful dissection.

Comment.—So far there has been no recurrence.

Case 3, coloured female, aged 20, on March 3, 1948, had painful swellings the size of an egg on the left wrist, hand, and fingers. These swellings had first been noted 3 years previously, and had remained unchanged, except for pain during the last year, especially after scrubbing.

Three years previously the patient had been in bed with "rheumatism" for 6 months, and swelling of the right wrist had been treated by "injections".

For the past year she had noted the onset of flexion contractures of the little and middle fingers at the proximal interphalangeal joints of both hands. The involved joints had never been painful or swollen.

Radiological Examination.

March 8, 1948: irregularity of outline of distal ulna and radius, and a curious beak-like projection distal to the semi-lunar in the lateral.

Laboratory Findings.—Urine and blood count normal. Sedimentation rate 38 mm./45 min. Kahn test negative. Tuberculin test negative.

A diagnosis was made of possible fibroma or lipoma of the tendon sheath.

First Operation.—A curved incision 4 in. long was made, originating over the dorsum of the second metacarpal and extending to about 1 in. above the ulnar styloid. The subcutaneous tissues were divided and the tumour mass dissected out. It was found to be constricted by the dorsal carpal ligament, located in the tendon sheath, completely encircling all the extensor tendons. It was impossible to remove it completely because of the extensive bleeding, since no tourniquet had been used. There were areas of cystic degeneration, the cysts being filled with greenish viscid fluid. The tendons incorporated in the mass showed villous surface growth and were dissected free as far as possible. The dorsal retinaculum was approximated and the hand placed in a moulded plaster-of-Paris splint.

Fluid recovered from the cystic areas showed a moderate amount of white cells, but no bacteria. The culture remained sterile for 48 hours.

Pathologist's Report (Dr. Jaffe).—Tendon sheath tissue shows delicate villous hypertrophy. Microscopic sections show sub-acute and chronic tenosynovitis suggesting rheumatoid tenosynovitis.

Later Developments.—The post-operative course was uneventful, but there was a painless recurrence of the mass on the dorsum of the left hand. It was about 4·5 × 9 cm., and apparently involved the sheath of the extensor communis digitorum as well as that of the abductor longus and extensor brevis. The skin over the swelling was warm and appeared doughy and cystic. The volar surface of the hand was not involved (Fig. 1).

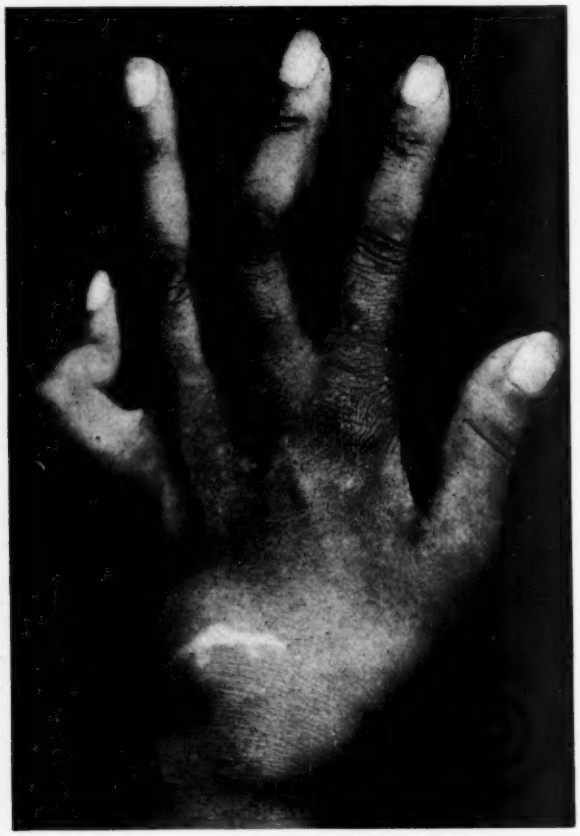

Fig. 1.—Case 3. Appearance of left hand following recurrence of symptoms.

Radiological Examination.

Wrists: slight irregularity in cortices of radii bilaterally at level of styloid process.

Carpal bones: normal.

Knees: large effusion in suprapatellar pouches.

Left tibia: subcondylar resorption in external condyle.

Right tibia: subcondylar resorption on outer aspect of external condyle.

Laboratory Findings.—Sedimentation rate (December 14, 1949), 72 mm./45 min. Non-protein nitrogen, 43 mg. Total protein, 8·4 per cent. Cholesterol, 169; free cholesterin, 27 per cent. Tuberculin test negative. No anaemia. No sickle cells. Fluid from cystic areas negative for tubercle bacilli, sterile after 48 hours. Guinea-pig negative for tuberculosis. Rosen test negative.

Second Operation.—This was performed with a pneumatic tourniquet. Through a 6-in. incision, the previous scar was excised. A cystic, irregular, greyish, boggy mass was found extending from the middle of the dorsum of the left hand to about 2 in. above the extensor retinaculum, superficial to the deep fascia. It was undermined and separated from the deep fascia from the proximal area down to the extensor retinaculum, where it was found to adhere intermittently to the extensor retinaculum, and to dip through it. When the muscles were exposed, this greyish mucoid granulation tissue was found to encompass the distal ends of the muscles, and the tendons of all the extensor muscles, including the pollicis longus, were also involved. The mass was dissected out from the tendons and cleaned down to the mid dorsum, removing with it the extensor retinaculum (Fig. 2, opposite). The tendons were thin and attenuated. A fascia lata graft was applied in place of the extensor retinaculum. Layer-by-layer closure was done and a cockup splint applied.

The fascial graft was extruded on the seventh post-operative day. The rest of the incision healed by primary intention.

Pathologist's Report (Dr. Jaffe).—A frayed cyst-like structure roughly the size of a goose egg. The cyst had been opened in many places. The wall was fibrous and in many areas villous hypertrophy of the synovial lining was noted. Sections of the synovium showed villous hypertrophy and cellular hyperplasia, with many focal areas of lymphocytic infiltration as well as acute exudate. The muscle showed focal lymphocytic infiltration.

Comment.—In the light of further experience we believe that had the first operation been performed with the use of a pneumatic tourniquet, the chances of recurrence would have been lessened or even eliminated.

The patient was last seen on February 26, 1951, when there was excellent function of all the extensor tendons and no sign of recurrence.

Case 4, coloured female, aged 63, first seen in 1945 with multiple joint lesions due to rheumatoid arthritis of 25 years' duration, had been unable to walk for the past 2 years because of pain and stiffness about the right knee, and had been bedridden for 2 years. The right knee was swollen, and the skin temperature raised; the joint was held in flexion at 110°, and no active or passive extension beyond this was possible, except with great pain. The para-articular structures were enlarged, though only a moderate amount of fluid was noticed in the joint. With the exception of the temporomandibular joints, all were affected to some degree.

Laboratory Findings.—Sedimentation rate 72 mm./1 hr (Westergren), marked secondary anaemia, Wassermann negative, serum protein normal, blood calcium 7, phosphorus and phosphatase normal, blood uric acid 4/1 mg. per cent.

Therapy.—Gold salts were administered and the patient's anaemia corrected; the contracture and acute inflammatory lesion of the knee was treated partly by

Fig. 2.—Case 3. Proximal portion of extensor tendons being freed from collagenous mass. Distal parts of same tendons are still enveloped by the mass.

traction and partly by manipulation, and a plaster-of-Paris encasement was applied with the knee in the position of 175°. The patient started to walk with the aid of crutches in one week after the application of the plaster, and finally made a satisfactory recovery.

Later Developments.—Two years later she reported a swelling on the dorsum of the left hand. This had increased gradually and become very painful during the past 2 months; it has been diagnosed as a ganglion and excision recommended, but we thought it was a collagenous soft tissue mass of rheumatic type, and the involvement of the tendons of the common extensor was quite obvious clinically.

Operation (February, 1947).—The gross and microscopic findings were the same as in previous cases, but cystic degeneration with accumulation of fluid was perhaps more prevalent. A pneumatic tourniquet was used and complete removal obtained by sharp dissection.

Comment.—The patient was seen last in January, 1951; the other lesions had progressed considerably, but there was no sign of recurrence of the hand lesion.

Case 5, white male, aged 29, who had been working 2 years before as a lumberjack, was first admitted on June 18, 1949, with painful swelling of the right hand; this had begun 12 months before but had only been painful for 6 months. A mass the size of an egg was seen over the dorsum of the right hand at the level of the radial styloid; whence it extended 2 in. proximally and 3 in. distally in a fusiform fashion. It seemed to be firmly attached to the common extensor tendons. Wrist motions were free, except that palmar flexion was limited to about 80 per cent. of that on left side. The mass was painful upon pressure and active motion. The grasping power of the left hand was diminished, but finger motions were not impaired. A pre-operative diagnosis of ganglion of the right wrist was made.

Laboratory Findings.—Blood sedimentation rate 8 mm./45 min., red blood count 4,960,000, white blood count 5,500, differential count normal.

First Operation (June, 1948).—No tourniquet used. Recovery uneventful.

Pathologist's Report (Dr. Jaffe).—Two pieces of tendon sheath ($3 \times 1\frac{1}{2} \times 1$ cm. and $4 \times 1\frac{1}{2} \times 1$ cm.). The inner surface was wrinkled and in places villously transformed. Parts of the inner surface were brown. A few tiny rice bodies adhered to the surface. Sections showed typical changes of rheumatoid inflammation, including

fibrinoid necrosis, rice-body formation, and rheumatoid nodule formation.

Later Developments.—He was re-admitted on November 7, 1949, 17 months later. Slightly tender fluctuant swellings were seen on the dorsum of the right hand and the anteromedial aspect of the right wrist, and a swelling over the dorsal aspect of the right ankle about half way between the lateral and medial malleolus corresponding with the tendons of the common extensors of the toes and peroneus tertius. No limitation of motion in the joints and no increase of skin temperature.

Laboratory Findings.—Sedimentation rate normal—6 mm./45 min. Wassermann test negative. No anaemia.

Second Operation.—Masses excised similar to those removed at previous operation. Tourniquet used.

Case 6, coloured female, aged 30, had noticed a mass on the dorsum of the right wrist for 3 years, since striking her hand against a sink. The mass had gradually increased in size for the past year with a mild and constant pain, and inability to extend the fingers fully. She had had a miscarriage in 1939, and a hysterectomy in 1942. There was no history of night sweats, weight loss, or known tuberculosis. On the dorsum of the wrist was a mass measuring $1\frac{1}{2} \times 1\frac{1}{2} \times 1$ in. It was a circumscribed, multilocular, cystic soft structure. The patient was unable to dorsiflex the wrist beyond the neutral position, or to extend the fingers except with the wrist flexed.

Radiological Examination.—*X* ray of the wrist taken immediately on admission revealed some asymmetry and spotty demineralization with relative increased densities at the styloid process of the radius.

Laboratory Findings.—Urine normal. Sedimentation rate 59 mm./45 min. Haemoglobin 9·8 g.

Operation (October, 1950).—A pneumatic tourniquet was used. The tumour, which involved the dorsal extensor tendons, was a reddish-yellow mass, and felt soft and meaty. There were numerous rice bodies, yellow, pebble-shaped masses with a very small amount of fluid, in a conglomerate gelatinous mass, through which the markedly frayed and atrophied tendons, quite adherent to each other, were shining as if they were made from wax.

It was not possible to differentiate macroscopically between collagenous disease and tuberculosis, but the latter now seemed most likely.

Pathologist's Report (Dr. Jaffe).—Microscopic examination revealed caseous and non-caseous tuberculous tenosynovitis.

Further Laboratory Findings.—Tuberculin test positive. Sputum was collected although the patient denied its existence and a few acid-fast bacilli reported on one occasion and negative findings on three others. Streptococcus agglutination positive 1 : 1,280. Wassermann positive.

Cerebrospinal fluid protein 21 mg. per cent., Kahn negative, colloidal gold normal, cell count normal.

Later Developments.—There was no primary healing of the operative incision. A sinus developed, but healed later. Diffuse swelling persisted in the operated area, but there was some improvement in the range of active extension of the fingers.

The patient next developed an acute exudative tuberculosis of the lung, and was transferred to another hospital for treatment.

Comment.—This case represents the only erroneous diagnosis in this series. It shows the difficulty of differentiating the collagenous tumours from tuberculous synovitis. Even at the time of operation it was not possible to make the correct diagnosis, notwithstanding that tuberculosis is always kept prominently in mind in dealing with the type of lesion. Had tuberculosis been diagnosed our surgical approach might have been modified by the simultaneous use of streptomycin.

Pathology

In exploring these lesions one is surprised by the extensive invasion of the surrounding tissues by the "tumour". It is particularly the tendon structure itself that is inseparably invaded, and it is hard to tell whether the growth originates in the epitenon or paratenon. The "tumour" tissue does not invade the subcutaneous or cutaneous structures, but does invade tendon and muscle tissue proper as is seen in the microscopic sections. The name *tenosynovitis* seems inadequate to describe these extensive lesions which far exceed the inflammatory character of tenosynovitis proper. This condition as found in the cases described above is invasive, expansive locally, and extremely cellular, and shows the characteristics of collagenous tissue. It is also destructive in that it destroys and replaces muscle tissue and diminishes the size of the tendons which become much thinner and seem to atrophy.

The gross surgical appearances differ depending whether a tourniquet is applied or not. When the tourniquet is used a greyish, almost rubbery, definitely soft, light-coloured mass bulges out, and is found upon dissection to follow the structure of the tendon sheath like a sleeve. If this tissue is incised right down into the tendon itself, it will be found that the tendon runs through it as through a tunnel and is closely adherent to it. Thus only meticulous sharp dissection will free the tissue from the tendon proper, and even so small fringes of the tissue will remain in places. These can be removed by rubbing with a dry gauze pad. In nearly every case the tendon itself was found to be almost half of its normal size. Fibrin (rice) bodies were present in half of the cases. Between the lobules of the "tumour" mass, there almost always appeared cyst-like structures filled with yellowish, turbulent, not very viscous fluid. When this fluid escaped during dissection, the mass, to some extent, collapsed. Two of these cysts were almost as large as

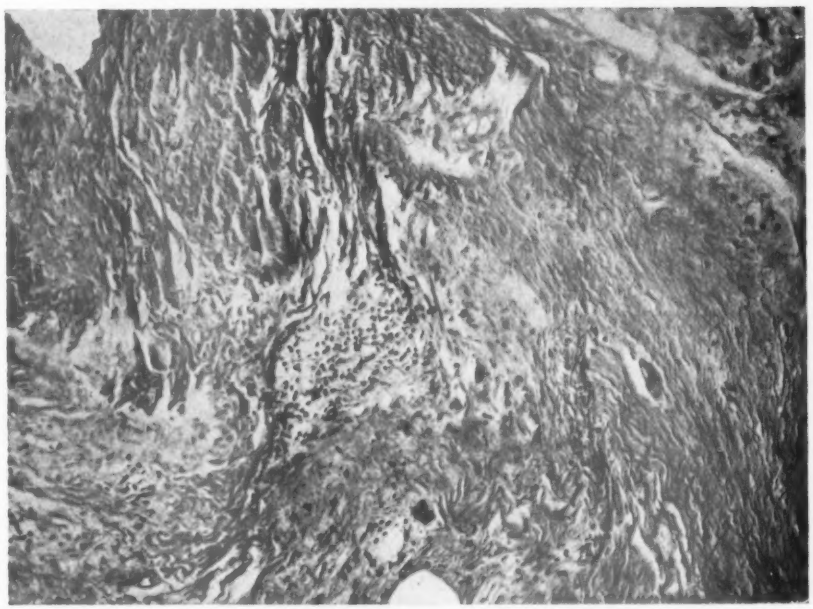

Fig. 3.—Case 5. Collagenous tissue with round cell infiltration and occasional giant cells. Case proven non-tuberculous. × 100.

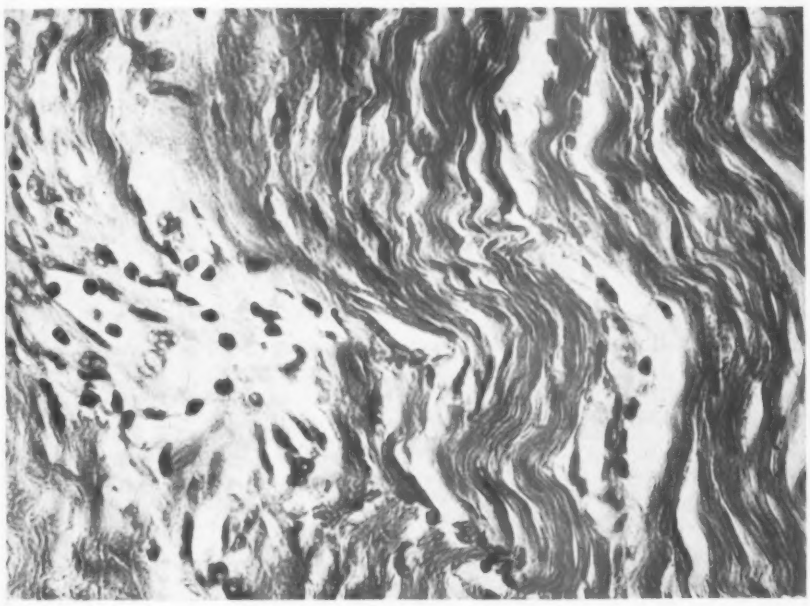

Fig. 4.—Case 5. High power view of section same case. × 250.

goose eggs (see Pathologist's Report on Case 3). The cysts had fibrous walls with villous hypertrophy of the synovial lining.

Microscopic sections show varying histological forms. At the synovial lining, villous hypertrophy with lymphocytes, plasma cells, and fibrinoid necrosis is prevalent. In the bulk of the tumour an immense number of collagenous fibres is the usual picture, and occasionally there are a great many fibroblasts and fibrocytes. Dark and light nuclei vary and giant cells with two to four nuclei are infrequently seen (see Figs 3, 4, and 5). In no instance (apart from Case 6) were these tissues tuberculous. Greatly thickened arterial and venous walls are commonly seen with para-adventitial lymphocytic infiltration.

Discussion

Diagnosis.—" Collagenous pseudotumour of the tendon sheaths ", or " tumorous rheumatoid tenosynovitis of the hand " has its importance as

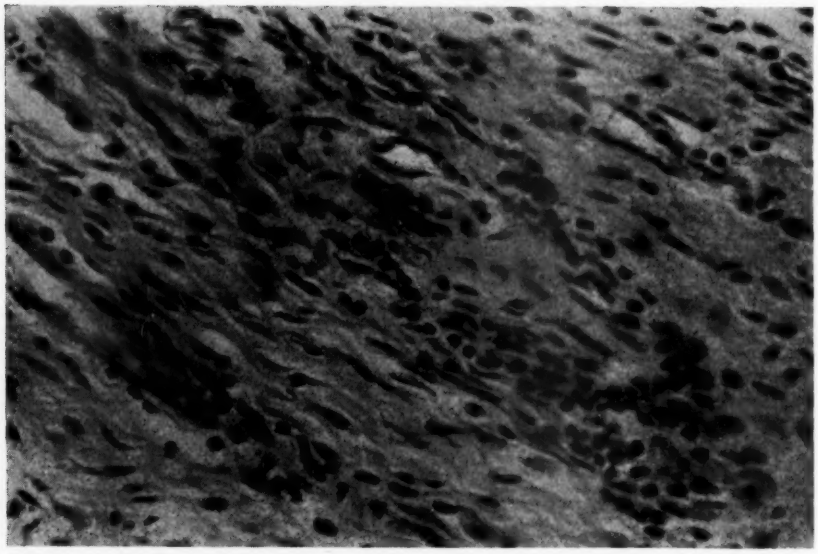

Fig. 5.—Section of mass excised from a seventh case, showing connective tissue with fibroblasts, fibrocytes and mild round-cell infiltration. × 125.

a diagnostic feature, and correct diagnosis will lead to correct treatment. During cortisone or ACTH administration these lesions regress temporarily but do not disappear. This is due partly to the absorption of the fluid in the cyst-like pouches in the lobulated mass, and partly to the elimination of the inflammatory changes.

Such tumours are by no means restricted to the hand, but this is their commonest location.

That such nodular tumours may be regarded as forerunners of generalized rheumatoid arthritis, was observed in two patients of the present series, and one other patient had such a lesion as the only rheumatoid manifestation in the tendon sheath of the tibialis posticus of the left foot.

X-ray Findings.—In all but two cases there were changes in the distal portion of the radius in the form of some irregularity, rarefaction, or atrophy. Circumscribed, " punched out " areas without the characteristics of gouty lesions were seen in the distal radius, the carpal, or the metacarpal bones and phalanges.

Nomenclature.—We have described these lesions as " tumours " because of their clinical and pathological features. There is little reason to describe them as examples of rheumatoid granulation tissue, and no evidence of pannus or necrosis.

Summary

(1) Six cases of tumorous tenosynovitis, rheumatoid in appearance, are described in detail.

(2) It is suggested that this clinical entity should be called " collagenous pseudotumour ".

(3) Reasons are given for drastic surgical treatment.

(4) It is reported that these lesions were not found to be improved by cortisone or ACTH, except temporarily and to a moderate degree.

My thanks are due to Dr. Isadore Zadek for his interest and co-operation.

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Pseudo-tumeurs collagènes des mains

Résumé

(1) On relate en détail six cas de ténosynovite tumescente d'apparence rhumatismale.

(2) On suggère que cette entité clinique devrait porter le nom de " pseudo-tumeur collagène ".

(3) On présente des raisons pour un traitement chirurgical drastique.

(4) On signale que ces lésions ne sont pas améliorées par la cortisone ni par l'ACTH.

Seudotumores colagenos de las manos

Sumario

(1) Se describe detalladamente seis casos de tenosinovitis tumorosa, aparentemente reumatoide.

(2) Se sugiere que esta entidad clínica debería llamarse " seudotumor colageno ".

(3) Se aduce razones para un tratamiento quirúrgico drástico.

(4) Se señala que estas lesiones no se vieron mejoradas con el tratamiento con la cortisona o la ACTH.

OSTEOPHYTOSIS OF THE LUMBAR SPINE

A COMPARISON BETWEEN THE INCIDENCE IN SASKATCHEWAN, CANADA, AND BRISTOL, ENGLAND

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The condition usually referred to as osteo-arthritis of the spine is extremely common and is usually diagnosed radiologically by the presence of spurs of bone arising from adjacent margins of vertebral bodies. The term osteo-arthritis is not desirable, as the joint between the vertebral bodies is a syndesmosis and the true diarthrodial joints of the spine are situated posteriorly. Recognizing this, workers have given the condition a variety of other names such as spondylitis, spondylitis deformans, spondylosis, and spondylosis deformans. Shore (1934) called it polyspondylitis marginalis osteophytica, but the simple descriptive term "osteophytosis" as used by Collins (1949) seems more satisfactory.

There is some doubt as to whether osteophytosis gives rise to any symptoms, but recent reports by Brain (1948), Knight (1948), Bull (1948), Spillane and Lloyd (1951), Bedford and others (1952), and other workers, suggest that it may sometimes be responsible for certain obscure myelopathies in elderly people. However, it is difficult to correlate such reports with the fact that the condition is demonstrated so frequently on routine radiography when there are no related symptoms. It is rarely found before the age of 40 years, but thereafter occurs with increasing frequency. The male sex is more frequently affected. Schmorl and Junghanns (1932) discovered spinal osteophytes in 90 per cent. of all men over 50 years of age, and in 90 per cent. of all women over 60; in the 4,253 spines dissected, the incidence was 10 per cent. in the third decade, 35 per cent. in the fourth decade, and 70 per cent. in the fifth decade.

Osteophytosis is found most commonly in the cervical and lumbar regions but the site of the lesion appears to bear no relationship to those intervertebral joints which carry most of the weight of the body (Shore, 1934).

There appear to be no reports available in the literature on the relative incidence of this condition in various parts of the world. It was noted that the presence of osteophytosis of the lumbar spine appeared to be extremely common in Saskatchewan, Canada. For this reason a detailed study has been undertaken to compare the incidence and severity in England and Canada.

Material

An unselected group of 961 *x*-ray films taken in Canada during the year 1950 was subdivided according to age, sex, and the degree of osteophytosis, and similar unselected series of *x*-ray films taken in England was subsequently assembled. The number and sex of the patients in each age group examined in Canada being known, an examination of routine films taken in England in 1949 was carried out in chronological order, until precisely the same number in each age group had been collected. Once the same number of examples in a particular age group had been seen, no further films in that group were included. This method ensured a random selection in both series. For the most part the films were those of city dwellers of a similar social class, but it was impossible to determine the occupation in each individual case.

Radiographs

It was found that a satisfactory view of the lumbar spine was obtained from examinations with the barium meal, barium enema, pyelogram, and straight *x* ray of the abdomen, and these radiographs were used in both the Canadian and Bristol cases. Films taken specifically to show the lumbar spine were not included.

Although the standards for the degree of osteophytosis are somewhat arbitrary, the same standards apply to both series, and the comparison was made within a period of 6 months by the same observer.

Minimal changes (±) were recorded when slight lipping or spurring occurred on the adjacent margins of one joint at one or both sides.

Definite changes (+) were recorded when spurring occurred at more than one joint, unilaterally or bilaterally, the spur not exceeding one-quarter of the breadth of the vertebral body.

Moderate changes (++) were recorded when the

spurring was present at more than one joint, the spur exceeding one-quarter of the breadth of the vertebral body but not exceeding one-half.

Gross changes (+++) were recorded when spurs were present at more than one point and exceeded one-half of the breadth of the vertebral body.

Using these standards little difficulty was experienced in deciding the degree of osteophytosis present.

Results

The results of this investigation are shown in the Table. Some observations of previous workers are confirmed by these findings. The condition appears earlier in the male sex and its incidence gradually increases with advancing age. Thus, in the 40 to 45 age group, 47 per cent. of males are affected and 31 per cent. of females. The number of males unaffected drops from 43 per cent. in the 40 to 45 age group to 2 per cent. in ages over 70, while the number of females unaffected drops from 69 per cent. in the 40 to 45 age group to 10 per cent. in the ages over 70. Females generally are not affected as frequently or as severely as males. Thus, in the 61 to 65 age group 67 per cent. of males show changes of + or more but only 41 per cent. of females.

The important finding in comparing the incidence of lumbar osteophytosis in the two countries is that the condition appears more frequently and more severely in the Canadian cases. In the 40 to 45 age group in the English series, 80 per cent. of males and 92 per cent. of females are unaffected, but in the Canadian series only 26 per cent. of males and 45 per cent. of females showed no change. In the 56 to 60 age group in the Canadian series 76 per cent. of males and 52 per cent. of females showed changes of + or more, while in the English series only 29 per cent. of males and 11 per cent. of females showed the same degree of change. In both males and females, in all age groups, the incidence of changes recorded as ++ or +++ is always appreciably higher in the Canadian series. Many more "gross" changes were seen in the Canadian series and this was particularly noticeable in the older age groups. These results confirmed the first impression gained in routine study of radiographs in Canada, where osteophytosis of the lumbar spine was so common that it was rarely considered worthy of comment by the radiologist reporting on the film. All differences referred to are greater than would be expected to occur merely by chance.

TABLE

PERCENTAGE DISTRIBUTION OF DEGREES OF OSTEOPHYTOSIS OF THE LUMBAR SPINE
(as judged by radiographs taken in Saskatchewan, Canada, and Bristol, England)

			40-45		46-50		51-55		56-60		61-65		66-70		71-75		Over 75		All Ages	
Age Group																				
Place			Can.	Eng.	Can.	Eng.	Can.	Eng.	Can.	Eng.	Can.	Eng.	Can.	Eng.	Can.	Eng.	Can.	Eng.	Can.	Eng.
MALES	No. of Patients		46	46	42	42	54	54	66	66	94	94	85	85	80	80	47	47	514	514
	Degree of Osteophytosis (%)	0	26	80	12	67	15	57	2	29	0	16	0	9	0	4	0	4	5	28
		±	46	20	57	31	28	22	23	42	14	37	9	31	5	29	2	40	20	32
		+	20	0	31	2	43	17	53	21	48	33	38	48	26	41	13	26	36	27
		++	9	0	0	0	13	4	18	8	34	13	39	12	43	20	49	23	28	11
		+++	0	0	0	0	2	0	5	0	4	1	14	0	26	6	36	6	11	2
	χ^2		30·556		29·586		23·624		34·130		38·458		41·508		35·126		34·218		177·2	
	n^1		2		2		3		3		3		3		3		3		4	
	p		<0·01		<0·01		<0·01		<0·01		<0·01		<0·01		<0·01		<0·01		<0·01	
FEMALES	No. of Patients		83	83	73	73	65	65	54	54	62	62	51	51	37	37	22	22	447	447
	Degree of Osteophytosis (%)	0	45	92	27	80	22	57	4	56	7	47	6	31	3	19	0	9	18	57
		±	43	8	51	18	43	31	44	33	19	36	14	49	8	35	9	46	33	29
		+	11	0	21	3	31	9	41	9	61	11	51	18	60	32	36	18	36	10
		++	1	0	1	0	3	3	7	2	11	7	28	2	19	14	36	27	10	4
		+++	0	0	0	0	2	0	4	0	2	0	2	0	11	0	18	0	3	0
	χ^2		43·018		40·920		18·964		39·594		44·572		39·528		15·858		10·476		179·132	
	n^1		2		2		2		2		3		3		2		2		4	
	p		<0·01		<0·01		<0·01		<0·01		<0·01		<0·01		<0·01		<0·01		<0·01	

Males: Additive $\chi^2=267·206$ $n=22$ $p=$less than 0·01.
Females: Additive $\chi^2=252·930$ $n=18$ $p=$less than 0·01.

Reasons for Differences

These differences are rather difficult to explain, particularly since the cause of spinal osteophytosis is in doubt. Shore (1935) suggests that ossification results from the strain put on the short deep intervertebral ligaments when the nucleus pulposa loses its normal elasticity and tends to bulge. This bulging occurs laterally owing to the weaker ligaments in that area. Collins (1949, p. 311) adds histological evidence that the ordinary osteophyte arises from the bulging of a collapsing disk.

Ageing.—Loss of elasticity of the nucleus pulposa is a normal ageing process which accounts for the prevalence of the condition in the older age groups. Bulging of the intervertebral disk occurs after the age of 40 and thereafter is a progressive process.

Trauma.—Shore also suggests that trauma may be an aetiological factor and that the condition may be related to the lifting of heavy loads. The occurrence of osteophytosis in the concavity of a scoliosis is constant and in this series of films many of the most gross changes were seen in association with scoliosis, particularly in the Canadian group.

Infection.—Toxic or infective factors have been suggested as contributing to the aetiology of this condition, but there is no evidence to support this.

Occupation.—There is no evidence that by habit or occupation the people of Saskatchewan are more exposed to traumatic influences than the people of Bristol. Although Saskatchewan is predominantly a wheat-farming province, the films studied were mostly from city dwellers.

Climate.—Climatic conditions, however, differ markedly from those prevailing in England, and it is possible that the extremely cold, dry winter, when the temperature drops to 40° F. below zero, the hot, dry summer when the temperature rises to 90°-100° F., and the dry centrally-heated homes, all help to cause the nucleus pulposa to lose its elasticity at an earlier age.

Drinking Water.—It is not possible to state with certainty that the figures given below represent the composition of the water used by all the patients in the two areas whose films were examined, but they are representative for the majority. Significant differences were found in the amounts of calcium carbonate (358 parts per million in Saskatchewan and 148 in Bristol), magnesium sulphate (277 parts per million in Saskatchewan and 5·4 in Bristol), and sodium sulphate (139 parts per million in Saskatchewan and nil in Bristol). It may be that the higher amounts of these substances in the Saskatchewan water supply make the osteophytosis more obvious.

Summary

(1) A comparison is made in the incidence of osteophytosis of the lumbar spine in a series of radiographs taken in Saskatchewan, Canada, and Bristol, England.

(2) The conclusion is reached that the condition appears more frequently and reaches a more gross degree in Saskatchewan.

(3) Suggestions are offered regarding the possible causes of the differences found.

I wish to thank Dr. A. E. Perry and Miss Joyce Berthiaume of the Regina Grey Nuns Hospital for their co-operation in finding the Canadian radiographs used in this investigation, Dr. J. H. Middlemiss, consultant radiologist at the Bristol Royal Hospital, for allowing me facilities to pursue the study in Bristol, and Mr. E. G. Whittle for supplying analytical data regarding the water supply. The statistical significance of the findings was analysed by Dr. E. Lewis-Faning, who has offered much helpful criticism.

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Ostéophytose de la colonne lombaire
Comparaison de sa fréquence à Saskatchewan, Canada et a Bristol, Angleterre

RÉSUMÉ

(1) On compare la fréquence de l'ostéophytose de la colonne vertébrale lombaire à Saskatchewan, Canada, et à Bristol, Angleterre, d'après les radiographies effectuées dans ces deux villes.

(2) On arrive à la conclusion que cette affection semble plus fréquente et plus prononcée à Saskatchewan.

(3) On suggère des raisons pouvant expliquer les différences constatées.

Osteofitosis de la espina lumbar
Comparación de su frecuencia en Saskatchewan, Canadá, y en Bristol, Inglaterra

SUMARIO

(1) Se compara la frecuencia de la osteofitosis de la espina lumbar en Saskatchewan, Canadá, y en Bristol, Inglaterra, según radiografías hechas en ambas ciudades.

(2) Se conclude que esta afección parece ser más frecuente y más pronunciada en Saskatchewan.

(3) Ofrécense sugestiones respecto a las causas posibles de la diferencias encontradas.

BLOOD GLUTATHIONE LEVELS IN RHEUMATOID ARTHRITIS

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 30, 1952)

It is well known that sulphydryl (SH) groups are necessary for the activity of important enzyme systems. Recent work by Rall and Lehninger (1952) indicates further, that the SH groups of glutathione play a direct part in electron carriage in cellular respiration. In view of the lesions found in the skeletal muscle in rheumatoid arthritis (Freund and others, 1945; Desmarais and others, 1948), we decided to ascertain whether the availability of the SH compounds of blood bore any relation to these rheumatoid changes. Preliminary experiments indicated that fluctuations in serum protein SH were too variable to relate to the clinical progress of the disease; this report concerns the glutathione content of the blood cells as this alone appeared to show some variation from normal.

Method

Blood analyses were first made by a nitroprusside method (Thompson and Watson, 1952) and later by an amperometric titration (Bidmead and Watson, 1952) which has been shown to give essentially the values obtained by the former procedure. Individual figures for glutathione sulphydryl (GSH) are accurate to $\pm$ 2 per cent. and the mean results calculated are for clarity expressed to the nearest mg./100 ml. The packed cell volume was determined in Wintrobe tubes, and the reading, without white cells, was recorded to the nearest 0·5 per cent.

Material

Venous blood was obtained from:

(*i*) a group of rheumatoid patients,
(*ii*) healthy subjects under 45 years,
(*iii*) cases of anaemia having no history of rheumatism.

The third group was subdivided into patients who had suffered loss of blood within a period of 7 days prior to blood analysis and those with a longstanding anaemia without demonstrable blood loss or gross sepsis.

Results

Table I confirms the existence of a raised red cell content of glutathione in chronic anaemia. The blood GSH concentration in these cases remains unaltered, but is considerably depressed in the acutely anaemic group.

TABLE I
MEAN BLOOD GSH VALUES IN ANAEMIC CONTROLS

Anaemia	No.	Packed Cell Volume	Blood GSH (mg./100 ml.)	Red cell GSH (mg./100 ml.)
Recent Blood Loss	7	31	22·5	73
Chronic (no blood loss)	4	28	31·1	110

In Table II the mean values for rheumatoid patients are compared with a healthy control group. GSH levels of the rheumatoid patients were in addition examined to see if any noteworthy correlation existed between these levels and the activity or duration of the disease, sex, or age. No significant correlation was apparent except in so far as:

(1) a slightly higher packed cell volume for men attends a proportionately lower cell GSH value than for women,

(2) cases with more highly active disease tend to have more severe anaemia and therefore a higher cell GSH content.

TABLE II
MEAN BLOOD GSH VALUES IN RHEUMATOID CONDITIONS AND HEALTHY CONTROLS

Disease	No.	Packed Cell Volume	Blood GSH	Red cell GSH
Rheumatoid Arthritis ..	65	40	32	80
Ankylosing Spondylitis ..	6	39	30	77
Controls	39	43	31	71

Table III gives the mean GSH concentration in the whole blood and red cells of rheumatoid patients with differing degrees of anaemia (as judged by haemoglobin levels). These results suggest that the severity of the anaemia has little effect on estimable GSH concentration in whole blood, but that a raised

erythrocyte GSH content is present in the more anaemic cases.

TABLE III

MEAN BLOOD GSH VALUES IN RHEUMATOID ANAEMIA

Degree of Anaemia	No.	Blood GSH	Red cell GSH
None	27	33	73
Slight	22	31	80
Moderate	16	30 (0·5)	92

A marked decrease in muscle GSH (in animals) and blood GSH in man (sometimes as much as 30 per cent.) has been reported following administration of growth hormone (Gregory and Goss, 1950), cortisone (Lazarow and Berman, 1950), and ACTH and hydrocortisone (Conn and others, 1948, 1949, 1951). A hyperglutathionaemia has been shown to follow the administration of DOCA (Binet and Poutonnet, 1943; Grunert and Phillips, 1949) and the production of an insulin hypoglycaemia in dogs. (Zunz, 1932—confirmed in our own laboratory in cases under treatment.) After administering ACTH, hydrocortisone, and cortisone acetate to three patients with rheumatoid arthritis, workers from the Mayo Clinic (Sprague and others, 1950) were unable to find any consistent pattern of change in blood GSH.

A number of estimations of red cell glutathione were made during the course of treating nine cases of rheumatoid arthritis with ACTH (100 mg. per day) and five cases with cortisone (200 mg. daily). In no case was a fasting glycosuria produced. No regular or consistent change in GSH level was found during the course of treatment. Two cases completely resistant to ACTH (Kersley and others, 1952) showed a slight degree of hypoglutathionaemia, but in the other cases no correlation between GSH levels and clinical response was found.

Summary

Using an improved method of estimation, erythrocyte glutathione levels in rheumatoid arthritis (before and after treatment) were investigated: no quantitative alteration attributable to the rheumatic process was found.

Any variations in GSH levels in rheumatoid arthritis appeared to be associated with the accompanying anaemia, and they support the haematological evidence already available (Jeffrey, 1952) that this anaemia is of haematopoietic origin rather than due to hydraemia. These results also agree with those of Joiner (1952).

Cortisone and ACTH produced no consistent changes in GSH, and when a slight depression of whole blood and cell glutathione occurred it was not necessarily related to clinical improvement.

We wish to thank the physicians and surgeons of the Royal United Hospital, Bath, the blood donors of the Royal National Hospital for Rheumatic Diseases, and members of this Unit for their co-operation.

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Taux sanguins de glutathion dans l'arthrite rhumatismale

RÉSUMÉ

Le taux érythrocytaire de glutathion (GSH) dans l'arthrite rhumatismale (avant et après le traitement) fut déterminé au moyen d'un procédé amélioré de dosage. On ne trouva aucune altération quantitative que l'on puisse attribuer au processes rhumatismal.

Toutes les variations du taux de GSH paraissent être liées à l'anémie accompagnant l'arthrite rhumatismale, ce qui vient à l'appui des données hématologiques existantes (Jeffrey, 1952) tendant à établir l'origine hémopoïetique plutôt qu'hydrémique de cette anémie. Ces résultats s'accordent aussi avec ceux de Joiner (1952).

La cortisone et l'ACTH ne provoquèrent pas d'altérations uniformes du taux de GSH, et de légères diminutions rencontrées dans le sang total et dans les éléments figurés ne furent pas nécessairement en rapport avec l'amélioration clinique.

Tasa sanguínea de glutation en la artritis reumatoide

SUMARIO

Se ha determinado, empleando un procedimiento perfeccionado de dosificación, las cifras eritrocitarias de glutation (GSH) en la artritis reumatoide, antes y después del tratamiento. No se encontró alteraciones cuantitativas que se pudiera atribuir al proceso reumatoide.

Todas las variaciones de la tasa de GSH parecen estar ligadas a la anemia asociada, lo que añade una prueba más a los datos hematológicos existentes (Jeffrey, 1952) que establecen el origen hemopoyético más bien que hidrémico de esta anemia. Estos resultados concordan también con los de Joiner (1952).

La cortisona y la ACTH no motivaron alteraciones uniformes de la tasa de GSH; las ligeras bajas de glutation que ocurrieron en la sangre total y en los glóbulos no estuvieron necesariamente en relación con las mejorías clínicas.

AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE ANNUAL MEETING, 1952

The annual meeting of the American Rheumatism Association was held at Chicago, Illinois, on June 6 and 7, 1952. The presidential address was delivered by Dr. Charles H. Slocumb of Rochester, Minnesota. Abstracts of the 26 papers and summaries of the discussions thereon are printed below.

One morning session was held jointly with the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association, and a Panel Discussion by the principal investigators of the United States and United Kingdom Co-operative Rheumatic Fever Study Group was held under the chairmanship of Dr. David D. Rutstein of Boston, Mass. (see p. 318).

Clinical and Metabolic Effects of Benemid. By JOHN H. TALBOTT, L. MAXWELL LOCKIE, BERNARD M. NORCROSS, and CHARLES BISHOP, *Buffalo, N.Y.*

Approximately fifty patients with gout receiving 1·0 or 2·0 g. Benemid daily have been followed for periods ranging from 6 to 24 months. The favourable results reported earlier upon the frequency of acute attacks of gout are confirmed. A persistent depression of the concentration of uric acid in the serum as well as an increased concentration of uric acid in the urine was noted. The body apparently did not develop tolerance to the pharmacological action of the experimental drug in the period of study.

The incidence of undesirable side-effects continued to be unimportant clinically. There was no greater tendency to uric acid stone formation, nor any occasion to discontinue therapy in patients in their second year of Benemid. The action of Benemid upon the metabolic pool and turnover rate of uric acid was studied. A depression in the metabolic pool persisted while the increase in the turnover rate remained within the normal range so long as the Benemid regimen was in force.

These studies lend support to the presumption that the action of Benemid is at the site of the renal tubule and is not concerned with the intermediary metabolism of purine bodies or of the precursors of uric acid.

Discussion.—DR. RICHARD T. SMITH (*Philadelphia, Pa*): We have been able to see a number of the results from all over the country on people who have been using Benemid. I am continually amazed after sending out information about the recommended dosage, to hear that Benemid is not well tolerated because the patient cannot keep it in his stomach when he takes 2, 3, and 4 g. daily. However, in most instances where the dose is kept no higher than 2 g., it has been well tolerated. The diagram (Fig. 1) shows the treatment of a patient who had had gout for many years and existed by adhering to a strict gouty diet, abstaining from alcohol, having physical therapy three times a week, and taking a large amount of colchicine, cincophen, and other drugs.

On June 15, 1950, he was started on Benemid. We then believed the minimal dose of Benemid to be 2 g. daily. The uric acid decreased immediately to 5·6 mg. per cent. and in 2 months went down to 3·6 mg. per cent. The dose was finally reduced to 1·5 g. with slightly better tolerance. Between June 15 and August 28, 1950, he had one long interval without an attack. Every time he took colchicine for an acute attack, however, he discontinued Benemid, although told to take it continuously.

Between September 1 and November 1, 1950, he had only one attack, and because of his freedom from joint disability and gastric intolerance of the drug he discontinued the medication. We saw no more of him until March 1, 1951, when he was given 1 g. Benemid daily and has continued this dose to the present time. After 4 months without therapy his blood uric acid level was only 7·3 mg. per cent.

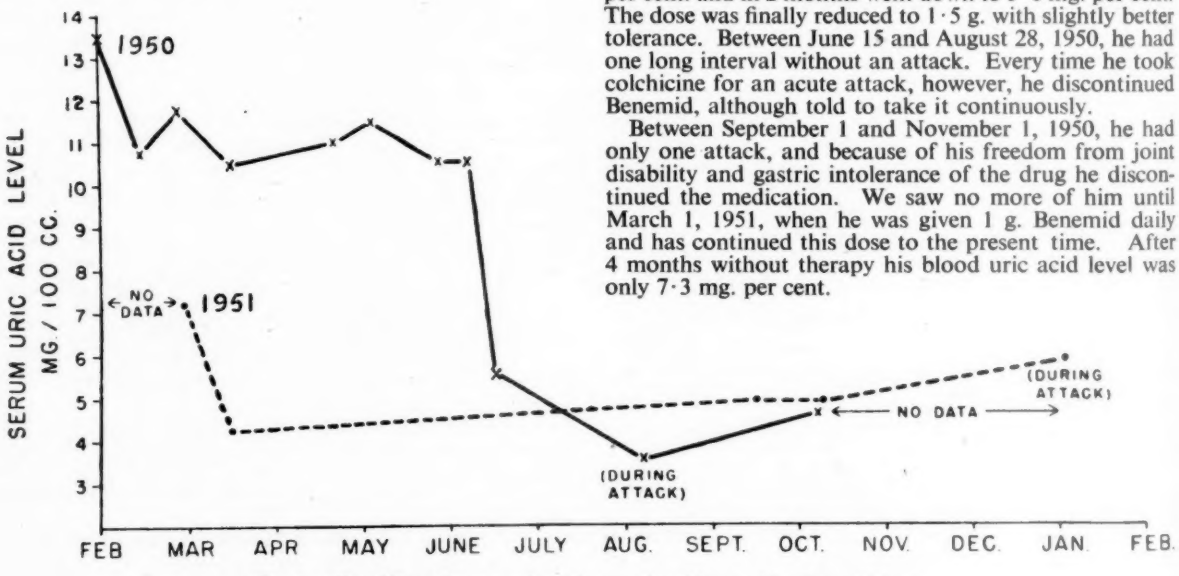

Fig. 1.—Use of Benemid as a uricosuric agent in a 54-year-old patient with gout.

The number of acute attacks have decreased, occurring only after prolonged severe physical exertion; he eats a normal diet, drinks alcohol occasionally, and tolerates Benemid well, and his blood uric acid has remained under 6 mg. per cent. During 1952 his blood uric acid has been less than 5 mg. per cent.

We believe that Benemid therapy reduces the number of gouty attacks, and makes patients comfortable and in some cases able to resume work.

DR. WILLIAM K. ISHMAEL (*Oklahoma City, Okla*): We started ten patients only, and it required about 6 months, using a 1 g. dose of Benemid to achieve a 37·5 per cent. drop in the uric acid levels.

DR. TALBOTT: I should like to close by stating that Benemid does not replace colchicine. We have been using colchicine with but few exceptions in the interval treatment of all patients with gout. During an acute attack colchicine is indicated whether the patient is receiving Benemid or not. Benemid is merely an adjunct and does not replace colchicine, except as an urico-suric agent.

Metabolic Studies in Gout with Emphasis on the Role of the Pituitary-Adrenal Axis in Acute Gouty Arthritis. By MELVIN H. LEVIN, J. BERNARD RIVO, and SAMUEL H. BASSETT, *Los Angeles, Calif.*

The adrenal function of seven gouty patients has been studied: eosinophil counts, urinary 11-oxysteroid excretion, serum and urinary uric acid, blood sugar, blood glutathione, and sweat electrolyte studies were performed during interval gout, acute spontaneous gouty arthritis, ACTH and testosterone administration, steroid-induced gout, and colchicine therapy.

Metabolic balances for N, Na, Cl, and K were performed in one patient for 90 days under the above conditions. A second patient and a normal control were studied for 161 and 59 days respectively, while on a chloride balance with observations of serum and urinary uric acid and circulating eosinophils. Basal observations plus the effects of mercurial diuretics and colchicine were made on the normal control. The effects of mercurial diuretics, colchicine, ACTH, and pitressin were studied in the gouty patient.

No evidence was uncovered to corroborate the hypothesis that acute gout is accompanied by a deficiency of adreno-cortical function. The association of acute gout with salt diuresis was inconstant. Fever and weight changes appeared to influence the electrolyte exchange. The metabolic response to ACTH was within normal limits. Colchicine regularly produced striking sodium and chloride retention.

Discussion.—DR. EDWARD F. HARTUNG (*New York*): This effect of colchicine in producing " a striking sodium and chloride retention " is most interesting, and may add to the information on the action of colchicine in the body.

Dr. Levin and his associates' work is somewhat at odds with the recent work of Dr. S. E. Dicker of University College Hospital, London, who showed in rats that after administration of colchicine there was a measurable increase in the renal excretion of water, with no effect on sodium or chloride excretion.

The effect of colchicine on water excretion is not a new observation. The Arabs used colchicum in dropsy, and Baron von Stoerck, who started the modern era of colchicum therapy, wrote on its use in dropsical conditions. Its effect in abnormal water retention has not recently been investigated, but warrants further study.

DR. WILLIAM D. ROBINSON (*Ann Arbor, Mich.*): The authors have made an important contribution to the confusing subject of metabolic disturbances in gout and their possible relationship to endocrine function.

I should like to ask whether any determinations of 17-ketosteroid excretions were made, and whether the determinations of the 11-oxysteroids made during the study showed any suggestion of rebound following the withdrawal of hormones.

Were the electrolyte changes observed, associated with expected changes in urine volume ? With the decreased electrolyte excretion we should expect water retention. Did this actually occur or was there a discrepancy between electrolyte excretion and total water excretion ?

I ask this last question because some observations suggest the possibility that posterior pituitary factors which can alter electrolyte excretion in relation to water excretion may be involved in some of these phenomena.

I should add that we have found no evidence that colchicine acts through the pituitary adrenal mechanism. All the evidence on that point is negative.

DR. WILLIAM R. MERCHANT (*Washington, D.C.*): That may be a peripheral action. We have carried out experiments on albumin for the last 2½ years. In using albumin, we had no results, but with colchicine the clinical results were rather dramatic, and one patient developed renal colic.

DR. LEVIN: In answer to Dr. Robinson, 17-ketosteroid studies were unfortunately not performed during this part of the experiment. We did have a random sampling of 11-oxysteroid excretion, but it was not made soon enough after ACTH withdrawal to determine whether full rebound activity could be determined by 11-oxysteroid studies as well as by the electrolyte balance.

We have data on the water balance with colchicine. Water retention occurred as well as retention of sodium and chloride.

Time did not permit discussion of the possibility of this being mediated through an ADH mechanism. An irregular line in the graph at the very end of the study was the effect of 0·5 ml. pitressin tannate in oil given intramuscularly. With this came a sharp change in water balance, and a slight change in sodium and chloride balance. With colchicine the opposite is true; here the effect is primarily on the electrolytes.

Lastly, none of our patients had renal colic when given colchicine.

Experiments in Repair of Articular Cartilage. By HANS WAINE and VAUGHN W. WESTERMEYER, *Boston, Mass.*

The reaction of articular cartilage was studied in adult rabbits with and without injection of purified growth hormone. The treated specimens differed from the controls in the response of cartilage to trauma, degree of spontaneous degeneration of cartilage, structure of the synovial membrane, and production of synovial fluid.

Discussion.—DR. G. A. BENNETT (*Chicago, Ill.*): Dr. Waine has undertaken to make an evaluation which all of us who have worked with this type of problem would agree is exceeding difficult.

In the first place, he is dealing with a type of tissue

which is remarkably inert in its ability to repair itself. Secondly, he is dealing with an anatomic area in which it is difficult to make reliable comparative observations. Thirdly, it is well known that variable responses, which cannot be correlated with any single factor of control, may occur in articular cartilage following injury.

I am impressed by the variable reactions of these, recognizing from what Dr. Waine has said that he interprets his material cautiously. This attitude is wise, I believe, because of the small number of animals studied and because of the known variations which can and do occur fortuitously in a series of cartilage lesions which are produced and maintained in the same way.

Dr. Waine's last example showed proliferation of cells, particularly deep down in the cartilage. If appearances of that sort can be obtained regularly and consistently after long periods of growth hormone administration, then one would be more confident of the effectiveness of locally applied growth hormone in promoting repair.

I should like to ask Dr. Waine whether or not this material has been tested on tissue cultures where cartilage was used as explants.

DR. J. ALBERT KEY (*St. Louis, Mo.*): These defects are so small. As I understand it, a cut was made in the surface of the cartilage. I was not able to detect much difference between the controls and the experimental knees.

I wish Dr. Waine had made a bigger defect and seen what happened. When cartilage is cut, especially in the rabbit, which in my experience reacts more violently than any other animal, the cells adjacent to the cut die and then those in the next layer proliferate, and the tendency is not only to heal but overheal. Over and above that, if the defect is of any considerable size there is also a proliferation of cartilage and bone around the margin of the articular surface so that newly-formed marginal osteo-cartilagenous masses are formed, and in rabbits those form quite quickly.

Cartilage cells that are exposed on the surface tend to die. The cartilage cannot heal because the cells are enclosed in lacunae. New cartilage or new connective tissue can grow between the cut edges and heal and cover over the defect area and in the depths of the cartilage the cells proliferate in the lacunae.

DR. RUTH SILVERBERG (*St. Louis, Mo.*): I think the significance of Dr. Waine's experiments lies not so much in the interpretation of individual histological details but in the fact that he has shown that hormones, and in particular pituitary hormones, exert an effect on the articular cartilage.

If we can show that a hormone, and in this case the pituitary hormone, may affect the cartilage, we may have opened a path leading to further research into the hormonal factors that operate in the pathogenesis of osteo-arthritis.

DR. HARRY A. FELDMAN (*Syracuse, N.Y.*): I should like to know whether the growth hormone was put in by injection, what the suspending material was, and whether the control knee received any similar type of manipulation,

DR. WAINE: Dr. Bennett's question about the use of growth hormone in tissue cultures of cartilage, I have to answer in the negative.

Dr. Key asked about the size of the defect. It was wedge-shaped, about 0·5 mm. wide on the articular surface, 0·5 or 0·75 mm. deep, and 0·5 cm. long.

I agree that chondrocytes react with some degree of proliferation to surgical trauma. However, we found as many as 32 nuclei in one lacuna in the col[illegible]nar zone of cartilage, a phenomenon not previously ob[illegible]ved either in relationship to superficial degenerative l[illegible]ions or experimental defects. Drs Ruth and Martin S[illegible]verberg, who are pioneers in the study of endocrine influ[illegible]nces on cartilage, wondered whether our work might [illegible]ave some clinical applications. This seems very questionable, because the tissue in the treated animals did not resemble normal cartilage, but showed a disrupted matrix.

As to the experimental procedure, may I repeat, that the control joints and the treated joints were handled alike, except that the injection into the right side contained the active principle, that into the left side the vehicle only. The hormone is soluble in salt solution at a *p*H of about 6·5.

***In Vitro* Fibrogenesis of Collagen.** By JEROME GROSS, *Boston, Mass.* (by invitation).

Fibrogenesis in general is of considerable significance, in that the existence of highly asymmetric molecules and aggregates make possible, among other more subtle, complex activities, both mobility and rigidity in systems composed predominantly of water. The nature and formation of fibrous connective tissue components, such as collagen, are of importance in embryogenesis, wound healing, and ageing, as well as in certain pathological and physiological states. Their study by *x*-ray diffraction and electron microscopy have furnished " finger prints " for collagen characterized by a typical wide-angle *x*-ray pattern and an axial repeating period of about 64 millimicrons with distinctive intra-period fine structure. Certain of the collagens, such as rat tail tendon, are soluble in dilute acid and form a fibrous precipitate on addition of salt. The demonstration of the normal collagen structure in reprecipitated fibres, the influence of ionic environment, serum acid glycoprotein, and other agents in the reconstitution of fibres from collagen solutions may point the way to a better understanding of the mechanism of fibrogenesis.

Therapeutic Observations on Butazolidin (Phenylbutazone) in some Arthritides and related Conditions. By OTTO STEINBROCKER, SIDNEY BERKOWITZ, SOLOMON CARP, MORTIMER EHRLICH, and MORTIMER ELKIND, *New York*.

Therapeutic trials of Phenylbutazone in a variety of articular and other conditions have been carried out for almost a year for short periods and in a long-term group. The project was conducted by a blindfold technique, with control studies of a placebo of similar appearance, as well as with salicylates, pyramidon, and gentisate. The objectives have been to evaluate the drug's analgesic properties, " anti-arthritic " action, and toxicity.

Of the entire group of patients tested, moderate to marked relief of pain occurred in an impressive percentage. In rheumatoid arthritis a small number of cases gave a Grade II or a Grade III response. Favourable effects occurred in ankylosing spondylitis, psoriasis with arthropathy, osteo-arthritis, and gout. The analgesic action of Phenylbutazone definitely exceeded that of any of the other substances.

A number of patients developed undesirable reactions, the untoward symptoms having consisted mainly in

gastro-intestinal or cutaneous reactions, or disturbance of the water balance (weight gain and oedema).

In spite of the fair number of reactions, Phenylbutazone promises to be a superior analgesic of real clinical usefulness in musculo-articular disorders, but with slight anti-rheumatoid action, if any.

Studies of Butazolidin and Butapyrin in Patients with Rheumatic Diseases. By E. C. KIDD, K. C. BOYCE, and RICHARD H. FREYBERG, *New York*.

Butazolidin or Butapyrin was given to approximately sixty patients with different types of rheumatic disease. When tolerated the medicine usually produced very good clinical improvement. Most consistent was the relief of stiffness and joint pain, which allowed significant increase in comfortable physical activity. There was no change in the erythrocyte sedimentation rate, even when good relief was maintained for many months.

Many patients had troublesome side-effects, chief of which were indigestion, with anorexia, nausea, bloating, sometimes typical ulcer symptoms, and often oedema. There were no instances of blood dyscrasia, or of reduction of circulating eosinophils.

Among the most remarkable effects was the quick arrest of acute gouty arthritis, which had sometimes been resistant to colchicine. In these patients there was prompt and significant reduction of plasma uric acid.

Stimulated by this consistent observation in gouty patients, measurements of blood uric acid were made in rheumatoid arthritic patients and these, too, were found to decrease consistently when Butazolidin was administered. These observations led to the comparison of uric acid metabolism in gouty and non-gouty patients receiving Butazolidin.

The effects of oral and intramuscular administration were also studied.

Discussion.—DR. W. PAUL HOLBROOK (*Tucson, Ariz*): I think that the last two papers are generally in accord with our own experience with Butazolidin. We have studied a total of 188 patients on Butazolidin, including 115 with peripheral rheumatoid arthritis, and 32 with rheumatoid spondylitis. The treatment period averaged 85 days; the largest group consisted of 36 patients who were on the drug for 150-455 days.

Results were similar to those reported, and rheumatoid spondylitis appears to be more favourably affected than peripheral rheumatoid arthritis.

Our experience in toxicity differs, however, from the reports given. In addition to the toxic manifestations reported, which we also observed, we saw rather striking drops in platelet counts and in haemoglobin. While on Butazolidin, platelet counts in 31 patients fell to below 100,000; and sometimes as low as 30,000-40,000. Eighteen patients had a significant drop in haemoglobin. The platelets appear to rise promptly on discontinuing the drug, but drop again when it is re-started. The haemoglobin recovery is somewhat slower. Two bone marrow studies were done at low platelet levels without finding any adequate explanation. So far we have not seen any serious haemorrhagic episodes with these low platelet counts, but we usually discontinued the medication when the platelet counts became very low. When medication was continued we have noted an escape mechanism by which the platelets appeared to rise again.

We are carrying out some metabolic studies with Butazolidin and are at present beginning to note blood and urine excretion levels. We feel sure that a re-evaluation of results will be necessary because we have noted that some of the oral tablets pass unchanged in the stools. Further information regarding absorption, excretion, and blood levels is necessary before any conclusions on the degree of anti-rheumatic activity of Butazolidin can be drawn. We are much interested in this drug and its relationship to rheumatic disease, and believe it warrants further careful study.

It takes courage these days and especially before this Society to report on a new anti-rheumatic drug, and I congratulate Dr. Steinbrocker, Dr. Freyberg, and their associates for such a discussion.

DR. WILLIAM C. KUZELL (*San Francisco, Calif.*): The results of studies done by our group, including Dr. Schaffarzick and myself, coincide approximately with those of the three previous speakers, especially Dr. Holbrook.

We feel that the most striking application of Butazolidin is in the treatment of acute gout and chronic gouty arthritis. The next most important applications are in acute bursitis of the shoulder, ankylosing spondylitis, arthritis with psoriasis, rheumatoid arthritis, and mixed arthritis (rheumatoid with osteo-arthritis). There is apparently no benefit whatever in simple osteo-arthritis.

Since October 9, 1950, we have treated approximately 550 patients; we have compared about 240 patients on Butapyrin (Irgapyrin) with Phenylbutazone, and find no essential difference in the long-term analysis of the results.

In addition to the toxic manifestations referred to by Dr. Holbrook, I should like to mention the incidence of severe stomatitis in twelve of our 550 patients. With the stomatitis there was no leucopenia, although it resembled that seen in agranulocytosis.

We had one case of agranulocytosis with Butapyrin and we now have one with Butazolidin, but both have responded rapidly to therapy when the drug was withdrawn.

We feel that agranulocytosis does not represent the hazard it once did, the real risk being that of non-recognition; in other words, the blood must be carefully studied at all times during administration.

We have also done extensive animal work. Since there was some clinical suggestion that Butapyrin (Irgapyrin) and Phenylbutazone might exert effects similar to those of cortisone and corticotropin (*e.g.* fluid retention and anti-rheumatic activity), they were tested experimentally.

First, the possibility of direct adrenal stimulation was investigated by the ascorbic acid depletion test, using hypophysectomized animals. While corticotropin significantly diminished adrenal ascorbic acid concentration, none of the pyrazolidins tested did so.

In the intact rat, furthermore, Phenylbutazone did not alter the adrenal ascorbic acid or cholesterol content. In Warburg's studies there was evidence that Phenylbutazone inhibited glucose utilization and oxygen uptake of brain slices.

In the experimental polyarthritis of rats (due to 'L' organisms) there was a slight worsening after using Phenylbutazone. The blood of 330 rats showed no change during a 4-month period of Phenylbutazone administration.

DR. EPHRAIM P. ENGLEMAN (*San Francisco*): Our experience has been confined to Butazolidin. We treated approximately fifty patients and the results were much the same as those described by Drs Steinbrocker and Freyberg.

Specifically, we were not impressed with the objective changes occurring during the administration of Butazolidin in patients with rheumatoid arthritis. Serial biopsy studies showed no effect of the drug upon the histological appearance of rheumatoid nodules. On the other hand, we were favourably impressed by its effects in gout.

We have completed one metabolic study in association with Dr. Peter Forsham, of the University of California, and our results confirm the observation that sodium is retained, that blood uric acid is decreased, and that there is no striking uricosuria. The last observation is of particular interest.

We observed one patient who developed agranulocytosis during treatment with Butazolidin, but with discontinuation of the drug and intensive symptomatic treatment, he recovered. Curiously, we were unable to reproduce agranulocytosis with the re-administration of Butazolidin, and for this we can offer no explanation.

An extremely interesting and provocative observation was made by Dr. Tom Green, of the medical house staff, and Mr. Bill White of our isotope unit, both of the San Francisco Veterans' Administration Hospital. They have shown that Butazolidin administered intramuscularly causes a marked reduction in the radioactive iodine uptake by the thyroid gland. Fig. 2 shows the effect of Butazolidin on I^{131} uptake by the thyroid gland in three patients. On the left control observations demonstrate normal I^{131} uptake in the euthyroid range. The patients were given Butazolidin 1 g. daily for 3 days. The drug was then discontinued and there was a marked and significant suppression in the I^{131} uptake. These observations have been confirmed experimentally by Dr. Kenneth Scott. Control rats showed a normal thyroid I^{131} uptake of 42 per cent.; after the administration of Butazolidin in what corresponds to a therapeutic dose, namely, 10 mg./kg., the I^{131} dropped to 1·4 per cent.

Fig. 3 (opposite) shows the effect in a patient with hyperthyroidism. The figures on the left show the remarkably high I^{131} uptake; those on the right show the sharp decrease in uptake after 3 days of Butazolidin 1 g. daily. We have not observed clinical hypothyroidism in euthyroid patients receiving Butazolidin orally over long periods of time. Whether this is because of inadequate blood levels, smaller doses, or a matter of thyroid escape, we do not know. Laboratory studies with regard to thyroid function in these patients are now in progress.

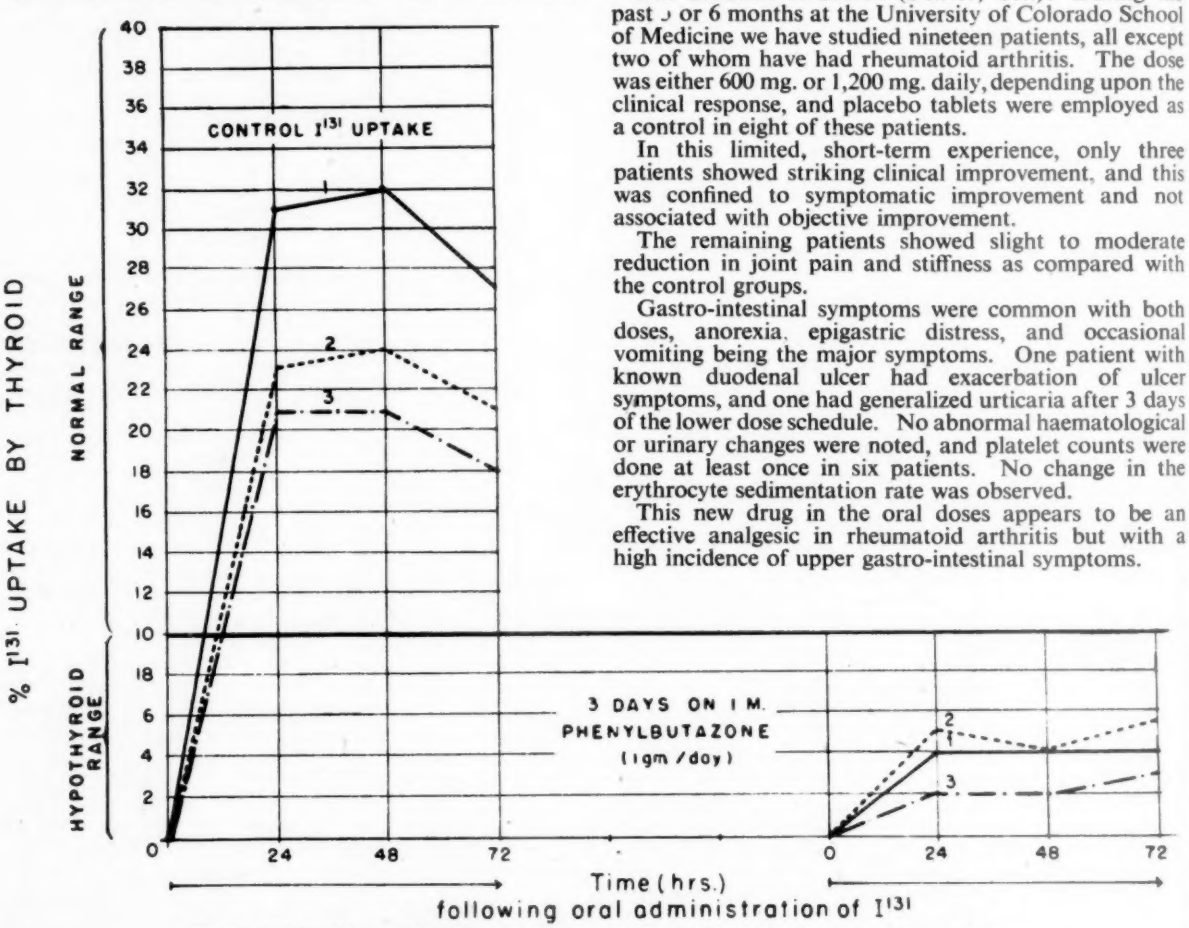

Fig. 2.—Effect of Butazolidin (Phenylbutazone) on I^{131} uptake by thyroid gland in three patients

1 —— 87 and 88 per cent. decrease in 24 and 48 hr. uptake.
2 ---- 77 and 83 per cent. ,, ,, 24 and 48 ,, ,,
3 —·— 90 per cent. ,, ,, 24 and 48 ,, ,,

DR. CHARLEY J. SMYTH (*Denver, Col.*): During the past 5 or 6 months at the University of Colorado School of Medicine we have studied nineteen patients, all except two of whom have had rheumatoid arthritis. The dose was either 600 mg. or 1,200 mg. daily, depending upon the clinical response, and placebo tablets were employed as a control in eight of these patients.

In this limited, short-term experience, only three patients showed striking clinical improvement, and this was confined to symptomatic improvement and not associated with objective improvement.

The remaining patients showed slight to moderate reduction in joint pain and stiffness as compared with the control groups.

Gastro-intestinal symptoms were common with both doses, anorexia, epigastric distress, and occasional vomiting being the major symptoms. One patient with known duodenal ulcer had exacerbation of ulcer symptoms, and one had generalized urticaria after 3 days of the lower dose schedule. No abnormal haematological or urinary changes were noted, and platelet counts were done at least once in six patients. No change in the erythrocyte sedimentation rate was observed.

This new drug in the oral doses appears to be an effective analgesic in rheumatoid arthritis but with a high incidence of upper gastro-intestinal symptoms.

DR. DAVID H. KLING (*Los Angeles, Calif.*): I am happy to confirm most of the findings of Drs Steinbrocker and Freyberg and their associates. I have treated 109 patients with tablets and/or intramuscular injections of Butapyrin and Butazolidin. The best results were obtained in eight cases of severe, active, ankylosing spondylitis (Marie-Strümpell disease) which had not yielded to any other treatment, including cortisone and roentgen therapy. Six patients had remissions or marked improvement within a few days. In this group, the erythrocyte sedimentation rate showed a significant average drop from 45 mg. to 25 mg./hr. (Westergren).

On the other hand, sixteen cases of advanced, active rheumatoid arthritis, refractory to other treatments, responded poorly. Only three were significantly improved, and in these treatment was soon discontinued because of reactions. In nine other cases of rheumatoid arthritis which had received cortisone and could not be maintained on a dosage less than 75-100 mg. daily, a combination with 2 or 3 tablets Butapyrin or Butazolidin was tried. In six patients an even better improvement occurred than on the higher dosages of cortisone given alone, but in two cases water retention increased and oedema developed.

Marked improvement occurred in sixteen (45 per cent.) of 33 patients with osteo-arthritis, in sixteen (63 per cent.) of 26 cases of fibrositis, and in eight (80 per cent.) of ten cases of neuritis and radiculitis.

It must be stressed that the beneficial results of these drugs do not persist after withdrawal except in conditions which have a natural self-limiting course. Reactions were encountered in 41 per cent. of the cases; 60 per cent. of them slight, 24 per cent. moderate, and 16 per cent. severe. The smallest number of reactions occurred amongst the patients with Marie-Strümpell spondylitis, and the highest amongst those with rheumatoid arthritis. The skin and gastro-intestinal tract were most frequently involved.

Butapyrin contains 125 mg. aminopyrin per tablet, and 750 mg. aminopyrin per 5-ml. ampoule. Therefore, one must be alert to the danger of depression of the bone marrow, especially of the granulocytes. Frequent blood counts have shown only occasional marked reduction in the total leucocytes and in the percentage of granulocytes. The eosinophils showed a moderate but constant average rise with both Butapyrin and Butazolidin, indicating that the reactions are of the allergic type. Indeed, the severest reactions occurred in an 82-year-old male after only six tablets of Butazolidin taken during a 3-day period. He ran a temperature of 102° F., a generalized exanthema, stomatitis, conjunctivitis, and anuria for 24 hrs. Although he had at first denied ever having had any history of allergy, close questioning of his wife brought out the fact that he had had skin reactions to other drugs. It is, therefore, important before administering these preparations, to exclude a history of allergy to drugs, even to those unrelated in composition to Butapyrin or Butazolidin.

DR. JOSEPH J. BUNIM (*Brooklyn, N.Y.*): Nothing has been mentioned of the effects of Butazolidin in acute rheumatic fever, and I wonder if anyone here has had experience with this drug in this disease.

We had an opportunity of administering Butazolidin in the usual 200 mg. four times daily to one patient with an initial attack of acute rheumatic fever with polyarthritis (temperature 104° F., and PR interval of 0·28). The temperature dropped to normal within 24 hrs., and the PR interval was reduced from 0·28 to 0·18 within 48 hrs. That may have been coincidental. The arthritis responded as dramatically as one would expect with an adequate dosage of salicylates.

DR. HARRY A. FELDMAN (*Syracuse, N.Y.*): May I answer Dr. Bunim? We treated ten patients with acute rheumatic fever with Butazolidin; nine children and one adult. Seven had carditis, as well as extracardiac rheumatic fever. We were unable to notice any effect whatever upon the carditis. The fever and extra-cardiac symptoms were controlled, although I think somewhat more slowly than with adequate doses of salicylates, but the patients went on to develop all the manifestations

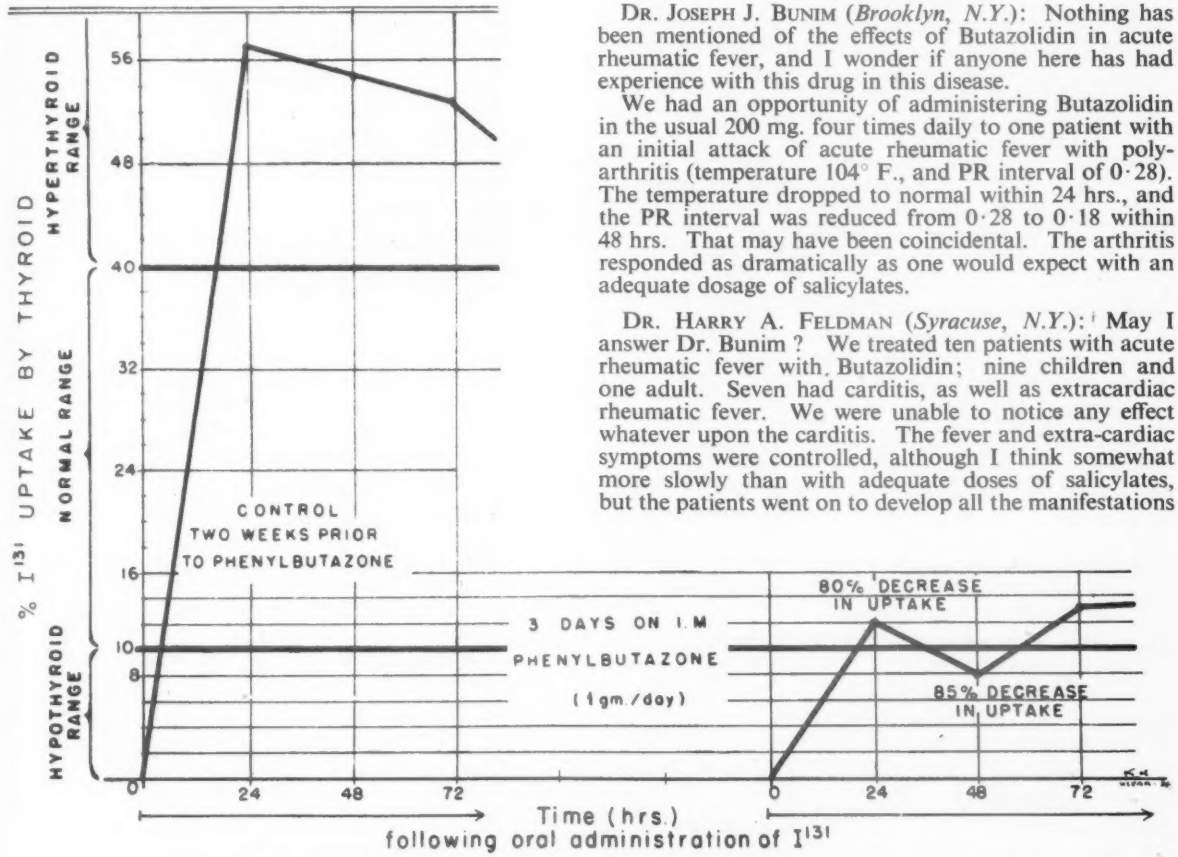

Fig. 3.—Effect of Butazolidin (Phenylbutazone) on I^{131} uptake by thyroid gland in a hyperthyroid patient

of valvular disease. One patient had intensification of his congestive failure, in spite of the fact that his salt intake was limited, and developed such profound azotemia that the drug had to be withdrawn.

DR. JOSEPH L. HOLLANDER (*Philadelphia, Pa.*): We treated 47 patients with Butazolidin and our results in the main are similar to those previously reported but with slightly higher incidence of toxicity. I want to give one warning: we treated two patients with disseminated lupus erythematosus with Butazolidin, and one developed agranulocytosis, which, however, responded to ACTH.

DR. STEINBROCKER: These drugs are far more interesting than we have been able to state in our limited remarks, both clinically and as regards their chemical effects which we had not time to discuss. There are many conditions which respond to them, several of which have been mentioned here; we have also had two recent cases of periarteritis nodosa which formerly responded to nothing short of ACTH and cortisone, which have now been excellently controlled for at least 4 to 6 weeks with Butazolidin. Our group rather suspects that the toxicity we have seen arises, first of all, from hypersensitivity, and secondly from dosage. I think much of this toxicity may be cut down by studying and reducing dosage.

DR. FREYBERG: We must all keep in mind that these are new drugs. More experience is needed before we shall know all we should like to know about their limitations and usefulness. The problem appears to be greater in chronic illness, when we need to use these drugs over a long period of time.

Also, with repeated use in patients with an episodic illness, such as gouty arthritis, we must keep in mind that sensitivity may develop in the intervals. We must keep a careful watch on those patients, particularly in regard to bone marrow damage and blood dyscrasia.

It is interesting to reflect on some of the information presented. For example, it was said that sodium, chloride and water were retained where colchicine and some other drugs, eminently helpful in quickly suppressing attacks of gout, were administered. It seems likely that the limits of usefulness and the manner of action of these drugs will be well defined in the future.

Evaluation of the Effects of Cortisone on the Subcutaneous Nodules of Patients with Rheumatoid Arthritis. By GRANVILLE A. BENNETT, SIMON ZIVIN, IRVING E. STECK, MAX M. MONTGOMERY, and GEORGE D. KAISER, *Chicago, Ill.*

Eight patients with rheumatoid arthritis were selected for study. Seven of the eight patients had paired, symmetrically-placed subcutaneous nodules. In seven patients nodules were removed before and after the administration of cortisone; in the eighth, only after cortisone had been injected.

After the removal of one of each pair of nodules in five of the eight patients, the remaining nodule was encased in a plaster cast which served as a permanent record of its size and configuration. Cortisone, 100 mg. daily, was administered intramuscularly for 8 days to one patient, 20 days to three, 22 days to one, 26 days to one, 3 months to one, and approximately one year to two. At the end of the observation periods, the size, shape, and consistency of the nodules were determined and another impression was recorded in a plaster mould for each of the same five patients.

The impression was received that all nodules became softer during the administration of cortisone. In four of the five instances in which comparative volumetric measurements were made by the mould impressions, the nodules had diminished in volume. The remaining nodules had decreased in size.

The nodule was then excised for microscopic examination. These studies comparing the histologic features of each of eight pairs of nodules revealed no consistent qualitative differences in encapsulation, inflammation, palisading of cells, or necrosis, that could be attributed to cortisone administration over the shorter period of time selected in this study. The degree of activity in three nodules removed after cortisone injection appeared the same as in the paired nodules excised before. In five instances, the degree of cellular activity and necrosis was greater in the specimens removed after cortisone had been given than it was in the paired nodules before cortisone was administered.

Discussion.—DR. METRO F. OGRYZLO (*Toronto, Ont., Canada*): A similar study was recently conducted at Sunnybrook Hospital, Toronto[1] and the pathological changes observed were more consistent than those reported to-day.

Six patients with active rheumatoid arthritis and multiple subcutaneous nodules were followed clinically while under treatment with either ACTH or cortisone. The subcutaneous nodules were followed by measurement, photographs, and repeated biopsies, and serial sections were then cut and stained with a variety of stains.

The changes appeared to follow a definite pattern. With the induction of a remission they quickly lost their tenderness and shortly after became softer and smaller in size. The initial decrease in size was obvious, but after a time further reduction ceased. At this stage the nodule might be quite soft and sometimes fluctuant. During the clinical relapse which followed withdrawal of hormone therapy, the nodules quickly increased in size, and would again become firm and tender. Occasionally new nodules might appear. In only one instance did a small nodule disappear entirely and not recur later.

Microscopically the observed changes also followed a constant pattern. The metachromatic staining properties of tissue undergoing fibrinoid degeneration disappeared early. This was followed by a decrease in the cellularity of the surrounding inflammatory reaction and eventually the palisaded layer of cells surrounding the central zone of necrosis disappeared. The necrotic areas showed less obvious change, although it appeared that the active process within the nodules had been stopped temporarily. With relapse, however, the classical pathological picture of the rheumatoid nodule reappeared.

It may be significant that the dosage of hormone in this study was larger than that used by Dr. Bennett. Most of our patients exhibited severe and advanced disease and large amounts of hormone were required to induce a remission. The treatment was directed at suppressing the inflammatory process and lowering the sedimentation rate to normal levels. The average daily dose of cortisone was 200 mg. orally, and that of ACTH 100-160 mg. intramuscularly during the induction of the remissions.

DR. J. ALBERT KEY (*St. Louis, Mo.*): Is there a parallelism between these nodules and the activity of the

[1] Hunt, T. E. and Blanchard, A. J. (1951), *Annals of the Rheumatic Diseases*, **10**, 337.

disease, and would you expect a change in the nodules because the symptoms of the disease had been allayed by cortisone ?

DR. CURRIER MCEWEN (*New York*): We have had several patients who have been treated for over a year and whose nodules have not decreased in size; and in one patient new nodules have actually appeared under therapy. Nevertheless the usual experience is that the nodules become smaller and disappear; for example, one woman with rheumatoid arthritis had many nodules in different parts, some almost as large as oranges, and most of them disappeared completely under therapy in less than 2 months.

On the other hand, in contrast to the decrease in size, the striking histological feature has been the absence of any significant change in appearance. The same is true of the nodules of rheumatic fever: in one boy a nodule removed after hormone therapy showed a great decrease in cellularity as compared with a nodule excised before treatment, but there appeared to be a concentration of fibrinoid material. We have not observed this in any other rheumatic nodules, however, and have had to conclude that it is not a common occurrence.

DR. BENNETT: We used toluidine blue as well as the periodic acid-shift reaction in trying to demonstrate changes in ground substance. However, we were unable to demonstrate any consistent changes in this material after the use of cortisone. One of the points I wish to make is that nodules are very complex structures and therefore, unless one evaluates the entire lesion, one may be badly misled by isolated variations in biopsy specimens.

When the entire lesions were examined, we found no consistent change in any component which could be attributed to the use of cortisone.

Not being a clinician I am not the person to answer Dr. Key's question. However, it is my impression that there is correlation between the activity of the nodules and that of the disease.

Gamma Globulin Specificity in Rheumatoid Arthritis. By J. H. VAUGHN, J. GOLDTHWAITE, P. BRACHMAN, A. ARMATO, C. B. FAVOUR, and T. B. BAYLES, *Boston, Mass.*

An investigation of the specificity of the serum proteins in rheumatoid arthritis has been undertaken. Gamma globulins isolated as Fraction II by cold alcohol precipitation (Cohn) and labelled with I^{131} have been used to trace the fate of these elements after intravenous administration ; and beta and gamma globulins, as Fractions III and II, have been studied in relation to possible adsorption by tissue stromata *in vitro*. Though there was a more rapid than normal rate of elimination of the injected material from the circulation by the rheumatoid group, there appeared to be no differential manner in which rheumatoid or normal gamma globulins were handled, suggesting that the proteins from these two sources are metabolized as structurally indistinguishable units. Scanning of the surface of the body after such intravenous injections has failed to show organ localization of the radioactive elements, and, within the limits of sensitivity of our methods, there is no evidence for specific uptake on to tissue elements *in vitro*.

These data provide partial evidence against the assumption that there is an immunological relationship between tissue proteins and serum globulin in rheumatoid arthritis.

Structure and Chemical Characteristics of Elastic Tissue. By ALBERT I. LANSING, *St. Louis, Mo.* (by invitation).

Although elastic fibres have a number of common features they differ significantly in different parts of the body, and even in a single locus they differ with age.

Elastin from the tunica media of old aortas is quite different from that from young aortas in amino acid composition, mineral content, specific gravity, and tinctorial reactions.

Skin from exposed parts of the body contains elastic tissue which changes with age (senile elastosis); it is quite distinct from normal dermal elastic tissue but is not the same as that found in ageing blood vessels.

Elastic fibres which have been exposed to a new enzyme, elastase, have been shown to contain an elaborate internal fibrillar structure.

Local Hydrocortisone in the Rheumatic Diseases: Summary of 17 Months' Clinical Experience. By ERNEST M. BROWN, JR., J. BRUCE FRAIN, LOUIS UDELL, and JOSEPH L. HOLLANDER, *Philadelphia, Pa.*

Evidence has previously been presented of a superior anti-rheumatic effect of hydrocortisone, compared with cortisone, when injected into inflamed joints. Preliminary clinical trials suggesting therapeutic usefulness prompted the extensive clinical experience now reported which included a critical assessment of therapeutic value, adverse reactions, and comparative effectiveness of the free alcohol and acetate of hydrocortisone, and of cortisone propionate.

In nearly 4,000 separate instances, hydrocortisone was administered locally to over 500 patients suffering from rheumatoid arthritis, degenerative joint disease, or other rheumatic disease. Intra-articular injections were made into any involved peripheral joints. Hydrocortisone was also introduced into various bursae, the pleural cavity, and the eyes of rheumatoid arthritics with ocular complications.

Therapeutic failure, as measured by indefinite or no improvement, occurred in approximately 10 per cent. Improvement of sufficient degree and of adequate duration to appear practical therapeutically occurred in about 90 per cent. An analysis of treatment failures is given. The only adverse reaction was a transitory exacerbation of symptoms and signs noted after about 2 per cent. of injections. The condition of one joint, later proved tuberculous, was probably aggravated by local hydrocortisone injection.

Effects on Intra-Articular Hydrocortisone Acetate on the Clinical Course, Aminotripeptidase Activity and other Changes in the Synovial Fluid in Rheumatoid Arthritis. By MORRIS ZIFF, EDWARD SCULL, DENYS FORD, CURRIER MCEWEN, and JOSEPH J. BUNIM, *New York*.

Hydrocortisone acetate (Compound F) was injected repeatedly into the knee joints of ten patients with rheumatoid arthritis. The clinical effect was evaluated and the changes in the physical, cytological, and biochemical properties of the synovial fluid were studied. In most patients both knees were involved; hydrocortisone or cortisone was injected into one, and a vehicle was injected into the other as a control. Whereas

intra-articular cortisone was followed by clinical improvement in a few instances, there was little doubt as to the consistent superiority of hydrocortisone. This difference was even more striking when changes in the synovial fluid was analysed. In every patient who received two or more injections of hydrocortisone there was a significant fall in the viscosity, leucocyte count, or concentration of aminotripeptidase; whereas such alterations were observed in only 25 per cent. of the cortisone-injected cases.

Discussion.—DR. IVAN F. DUFF (*Ann Arbor, Mich.*): We have made serial observations during repeated intra-articular injections of Compound F acetate at 3- to 7-day intervals in a number of patients with rheumatoid arthritis. In addition to suppression of inflammation, evidence has been accumulated of alteration in the physical characteristics of the synovial fluid.

In particular, viscosity of joint fluid has been determined by the technique already described. The concentration of hyaluronic acid has been determined turbidometrically. The validity of using the ratio

$$\frac{\text{log of viscosity}}{\text{polysaccharide concentration}}$$

to indicate the degree of polymerization of hyaluronic acid has been confirmed.

After intra-articular Compound F, this index of polymerization is increased, indicating that the increase in viscosity is not due only to changes in concentration of the polysaccharide. These changes were also observed with repeated daily injections of cortisone without clinical improvement. It is true, of course, that improvement in the characteristics of synovial mucin demonstrated by these two different methods may occur purely as a consequence of suppression of inflammation. However, it seems to be more than a simple anti-inflammatory effect and can be interpreted as evidence of a direct local effect of Compound F upon the altered chemistry of connective tissue in this disease.

A definite increase in the viscosity of joint fluid was observed in serial observations in ten out of twelve patients; increase from the initial low figure to values several hundred times greater were observed, as was an approximate doubling of the polymerization index. Repeated injections were associated with definite evidence of a cumulative effect, and correlation between clinical effectiveness and viscosity values was the rule. These changes may not be observed with the initial injections, and may not become marked until the second or third week of treatment.

Of the eighteen individuals with rheumatoid arthritis to whom we have administered intra-articular Compound F, six failed to demonstrate subjective or objective benefit with the initial injection and, in three, serial injections produced no response. Favourable subjective response was achieved in two with the initial injection but was not sustained.

All of the remaining ten patients demonstrated an initial favourable response to serial injections. Subjective improvement may occur within a few hours, but although objective improvement was sustained in a few instances for as long as 6 weeks, it usually subsided within a period of 3 to 7 days; in two patients, treated repeatedly for 6 months, the initial pattern of response was unaltered. This experience leads us to suggest that the value of serial injections of intra-articular Compound F acetate is apparent as a temporary source of improvement, and that in selected patients, it may aid in rehabilitation. The inability of the procedure to produce satisfactory long-term benefit was evident in patients whose disease was of considerable duration. In this group, the brief though reproducible clinical benefit within a variable period reached a plateau, beyond which we were unable to advance. We had no experience with intra-articular Compound F acetate in osteo-arthritis.

DR. MARIAN W. ROPES (*Boston, Mass.*): We have given 25 injections to sixteen patients, twelve of them rheumatoid, and our results were somewhat different. We also found that there was little evidence of systemic effect; this was only slightly suggested in two patients, and the variation in response was great.

We had an occasional extremely good subjective and fairly good objective response, but 20 per cent. of the rheumatoid patients gave no response at all, and 30 per cent. showed no objective response.

The synovial fluid changes observed were more consistent. I agree with Dr. Duff that the viscosity change is perhaps the most marked; in fact, we found it with intra-articulation of Compound E as well as Compound F. It is this fact that makes me wonder whether the effect of these steroids on viscosity and presumably on the polymerization of hyaluronic acid may not be separate from the anti-inflammatory reaction. There is very little proof of this, except for the fact that in a Charcot joint treated systemically there was no other change in inflammation, but a very marked rise in viscosity.

I have been impressed by the extreme dissociation between subjective and objective clinical findings, and the synovial fluid changes, and I should be interested to know whether others have made the same observations.

One of our patients had a 4+ subjective improvement after the first injection, which has been maintained for 3 months, and yet she has not had any lasting objective clinical change. In two others the fluid response was the best we have noted, and yet they had no objective clinical changes in their joints.

I think that the intra-articular injection of Compound F can produce a very marked anti-inflammatory action, but this is not produced in all joints, and the duration of improvement varies from joint to joint, and from patient to patient. We have also had some experience of a suggestion that the inflammatory process has progressed in some cases during the course of treatment.

In one patient, fluid obtained 2 months after the first of a series of monthly intra-articular injections showed changes much worse than those present before the treatment was started. The sugar concentration had dropped from 40 to less than 5 mg., and the mucin precipitate which had been shreddy and somewhat cloudy had disappeared entirely. One cannot yet be sure whether this was connected with the treatment. Furthermore, two patients showed a tendency towards a less good fluid response after repeated injections.

DR. RALPH A. JESSAR (*New York*): We have studied the changes in joint fluid after intra-articular Compound F acetate, and all our patients showed a definite beneficial effect of varying duration characterized locally by decrease in pain, swelling and/or other signs of inflammation.

Seventeen sets of observations in six patients were made before and 2 to 7 days after treatment. We measured the total protein, relative viscosity, and hyaluronic acid concentration. From the last two

figures a factor was derived to express the degree of polymerization of the hyaluronic acid present in the synovial fluid, an increase in this factor reflecting the presence of a more highly polymerized hyaluronate.

Our preliminary studies reveal that after the local use of Compound F in the knees, no definite pattern of response was noted in the total protein. In ten instances an appreciable increase in relative viscosity was apparent, and in nine this was accompanied by a rise in hyaluronic acid concentration, which did not, however, vary proportionately with the log of the viscosity. Hence, in the ten pairs of observations noted, an increase in the factor was seen in eight, a decrease in one, and no change in the other.

Four pairs of fluids were examined electrophoretically; these studies reflected the same changes as shown by the measures of total protein and hyaluronic acid. In three of the pairs a 20 to 25 per cent. decrease was seen in the total area of electrophoretic pattern after Compound F as compared to the pre-treatment pattern. In each case a fast-moving component, which has the mobility of hyaluronic acid isolated from synovial fluid, was seen, and this remained the same or increased slightly after treatment with hydrocortisone.

Although the beneficial clinical effect of Compound F was generally quite striking, there was no consistent change in the joint fluid total protein, viscosity and hyaluronic acid concentration. In ten out of seventeen observations we found that the most apparent change was an increase in the relative viscosity paralleled by increases in hyaluronic acid and in the polymerization factor. These studies shed little light on the mechanism of the local action of Compound F.

DR. J. ZUCKNER (*New York*): Our experience of the local administration of hydrocortisone acetate has been with 746 injections given to 81 patients (39 with rheumatoid arthritis, 28 osteo-arthritis, and 14 with miscellaneous conditions including intermittent hydrops, pigmented villonodular synovitis, subcutaneous nodules, and bursitis):

(1) 61 rheumatoid joints were treated, 42 being knees, and 82 per cent. were studied for a more than 30 days, seven joints for more than 300 days.

Subjective improvement greater than 50 per cent. was reported in 70 per cent. of the injected rheumatoid joints; and an estimated objective improvement greater than 50 per cent. occurred in 51 per cent.

In many rheumatoid joints subjective improvement greater than 50 per cent. has been sustained. Improvement was maintained without further injections for more than 60 days in 31 per cent. of the joints, for between 15 and 30 days in 24 per cent., and for less than 14 days in 32 per cent. The objective findings paralleled the symptomatic improvement.

(2) 36 osteo-arthritic joints were injected in 28 patients (15 hips, 19 knees, and 2 fingers). Subjective improvement greater than 50 per cent. occurred in eleven out of nineteen knees, but in only four out of fifteen hips. Thus the results in osteo-arthritic knees and fingers generally paralleled those observed in rheumatoid arthritis, but in the osteo-arthritic hips results were generally poor.

In attempting to formulate a simple plan for injections, the dose was varied from 25 to 100 mg., and the interval between injections was changed systematically. This study showed that each patient requires to be treated individually because of the variability of response. Most patients derived significant improvement from 25 or 50 mg. injected at intervals which were best determined by the degree and duration of the relief experienced, varying from 7 to 30 days. An occasional patient will do better on larger doses or with infrequent injections.

DR. CHARLES L. STEINBERG (*Rochester, N.Y.*): I have a case history to illustrate a point which I should like to make: A neurosurgeon was seen at 1 p.m., with all the signs and symptoms of acute subacromial bursitis of 24 hours' duration. A dose of 37·5 mg. hydrocortisone was injected into the bursa and 2 hrs later he was able successfully to complete a complicated neurosurgical procedure. The next day the pain factor was still absent although there was some limitation of motion of the shoulder joint. He was given 40 units corticotropin, and the following day had practically normal motion of the shoulder joint, and no pain. Another 40 units corticotropin were given, and the following day all the signs and symptoms of the condition had disappeared.

Here we have a self-limiting condition, namely acute subacromial bursitis, in which one of the prime indications for the trial of hydrocortisone was in order.

We have also completed the study of 25 cases of acute subacromial bursitis, all of whom were successfully treated, apart from two who had a recurrence after excessive exercise. Two patients of the so-called chronic type and one patient with the shoulder-hand syndrome were failures.

We think the optimum dose of hydrocortisone is 37·5 mg., and that the so-called secondary fibrositic signs and symptoms that remain—i.e. lack of motion—are best handled with corticotropin, provided there is no contraindication.

We may wonder why such an acute process can be so easily reversed. Several speakers have suggested a possible change in chemistry, which seems very plausible. Possibly some change in the local enzymatic reaction occurs, but this does not explain why seven patients with acute subacromial bursitis who were treated intramuscularly with 40 units daily corticotropin for one to three days have had similar results.

The effects of corticotropin are not so rapid; relief usually occurs 3 to 6 hours later after hydrocortisone when it may occur within a few minutes.

DR. ROLAND DAVISON (*San Francisco, Calif.*): I think it is time to remind you that there are some dangers in this type of therapy. This material is now available to general practitioners, and I fear it will be used in the treatment of rheumatoid arthritis without the addition of other therapeutic measures.

Our experience has been limited in rheumatoid arthritis to patients with certain specific changes in the joints, and we used it only as an adjunct, chiefly in knees, wrists, elbows, and shoulders, with the idea of increasing mobility of joint or suppressing effusion. We did not find it very beneficial in any of our patients; though many responded in the way that has been described, with temporary improvement, in none who had serial injections over a period of 3 months did this improvement persist. Consequently, we feel that we should approach the use of hydrocortisone in rheumatoid arthritis very judiciously.

As regards patients with osteo-arthritis on the other hand we feel very differently. Here we are dealing with an older age group who have certain degenerative changes; we have felt it safer to use this material, without fear of late effects and have found it very helpful in controlling their symptoms.

DR. DAVID H. KLING (*Los Angeles, Calif.*): In the discussion of a paper on the "Comparative Effects of Compound F and Cortisone injected locally into the Rheumatoid Arthritic Joint" which was delivered by Dr. T. Hollander and his associates before the meeting last year, Dr. J. J. Bunim stated that:

> injection of 50 mg. cortisone acetate into the knee joints of twelve patients with rheumatoid arthritis resulted in eight in marked to moderate improvement locally.[1]

To-day Dr. Bunim's group claim that intra-articular cortisone was followed by clinical improvement in only a few instances, and by changes in the synovial fluid in only 25 per cent. I should like to ask what happened this year?

On the same occasion I myself pointed out that intra-articular injections of cortisone have a definite though transitory local anti-inflammatory effect. I, therefore, opposed Dr. Hollander's idea that cortisone has only a systemic effect, while Compound F exerts a powerful local action. Further experience with both preparations has not changed *my* position. Fourteen cases of rheumatoid arthritis with effusions of the knee joints alternately received 50 mg. cortisone or 50 mg. Compound F intra-articularly. In five cases the results were poor with both preparations; moderate improvement was obtained with cortisone in three, and with Compound F in two cases. Significant improvement occurred with cortisone in six, and with Compound F in seven cases.

Last year Dr. Hollander, in his closing remarks, stressed that:

> "We do not claim that Compound F used locally is a treatment for rheumatoid arthritis . . ."[2]

Now he and his group propose this preparation for the therapy not only of rheumatoid arthritis, but of osteo-arthritis and other non-inflammatory joint conditions, with and without effusions. I have given Compound F in various dosages in twenty cases of the latter types of arthritis. The results were poor in eight; moderate improvement was obtained in six cases, and marked improvement in six. Evaluation of results in these non-inflammatory types is even more difficult than in rheumatoid arthritis. Changes in the composition of the synovial fluid cannot serve as a control as in rheumatoid arthritis, because in osteo-arthritis the effusions contain a low total cell count and a low percentage of granulocytes, and their viscosity is high to start with. The skin- and intra-articular temperature is not elevated and the results can, therefore, only be judged clinically. The natural course of osteo-arthritis and other non-inflammatory joint affections is even more unpredictable than that of rheumatoid arthritis. Effusions in osteo-arthritis are frequently liable to disappear spontaneously, and aspirations alone have resulted in prolonged absorption in 45 per cent. Only extensive, comparative studies which take into account all the complicating factors will lead to a sound basis of evaluation of intra-articular therapy with Compound F and other steroids. The idea that therapeutic intra-articular injections in osteo- and other forms of arthritis are new is erroneous. Different solutions including Novocain, iodine, Lipiodol, and vaseline have been extensively used, and mostly forgotten, since the latter part of the 19th century. It is unfortunate that exaggerated reports in the lay press have added a disturbing factor which jeopardizes the unbiased evaluation of intra-articular injections of steroids. Such publicity should be opposed by this Association in the interests of the patient as well a of medical practice and research.

DR. WILLIAM B. RAWLS (*New York*): We have treated 75 patients with rheumatoid arthritis who did not react well to cortisone with 474 injections (155 into knee joints, 23 into wrist joints, 4 into hips, 6 into subacute and acute subacromial bursitis, and over 200 into phalangeal and metacarpal phalangeal joints). We have had reduction of swelling, increased motion, and return of function in many joints.

In patients with Heberden's nodes, where we had evidence of inflammatory reaction, redness, soreness, and pain, intra-articular injection caused the disappearance of this pain and discomfort, and brought the joint back to function.

We treated fifty patients with rheumatoid arthritis, mainly in fingers, wrists, and elbows, and have had about the same results with the fingers as have been reported with other joints.

DR. PAUL J. BILKA (*Minneapolis, Minn.*): We have heard a great deal about clinical and objective estimates of improvement, but how about biopsies? Has anyone found any correlation with objective and subjective improvement, indicating any changes in the synovium?

We have just started work on these lines with three patients, and I have been able to observe little change, despite marked objective and subjective changes at the time of the second biopsy.

DR. SCULL: I can answer that last question. From one biopsy taken after four injections of 50 mg. Compound F at 3-day intervals, there was no alteration in the pathological sections of the synovial membrane.

DR. J. ALBERT KEY (*St. Louis, Mo.*): Apparently these observers put suspended material into the hip joint, knee joint, or finger joint and it acts locally.

It seems to me that a knee joint with several hundred times the surface area of a finger joint would require a larger dose. Do they precede the injection with novocaine? Acute bursae sometimes recover promptly if punctured with a needle or injected with novocaine, while in others the same procedure is followed by severe pain which lasts for 48 hrs. or more.

It is, of course, difficult to inject a small amount of fluid (1 ml.) into a joint and to be sure that the material reaches the joint cavity.

DR. BROWN: I should like to pass to Dr. Hollander the question raised by Dr. Ropes regarding the percentage of instances in which good subjective results without demonstrable objective changes were elicited.

DR. HOLLANDER: We had probably 15 per cent. of patients who had objective change after injection of Compound F, but who would be recorded as marked subjective benefit; conversely, we had about 10 per cent. who obtained marked objective benefit with little subjective relief.

In some cases the swelling would disappear completely with hardly any improvement in the amount of pain. I agree that the variation in degree and duration of response is tremendous.

DR. BROWN: Early in our joint paracentesis experience we found that preparation of the over-lying tissues with a local anaesthetic was of little use. When we used

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[1] *Annals of the Rheumatic Diseases* (1951), **10**, 474.
[2] *Ibid.* (1951), **10**, 476.

1 per cent. procaine infiltration we found that the act of obtaining anaesthesia was considerably more uncomfortable than the simple and rapid plunging of the paracentesis needle directly into the joint space. Simple freezing of the over-lying skin with ethyl chloride offers little by way of anaesthesia, and is frequently attended by rather severe discomfort and superficial skin necrosis.

In answer to Dr. Key's question, our experience has shown excellent results with as little as 3 mg. in acutely inflamed finger joints; and we have on occasion used as little as 15 mg. in joints as big as knees and obtained the apparent maximum therapeutic response. Generally, however, the knees and other large joints require 25 mg., and it is rarely necessary to go up to 37·5 mg. to get the maximum response. I believe we found none who required as much as 50 mg., though we encountered no untoward effects when we used this much for one reason or another.

DR. ZIFF: In answer to Dr. Ropes's question about the relationship between synovial fluid changes and objective clinical improvement, I would agree that one is likely to see positive changes in the synovial fluid more frequently than one observes a positive clinical response.

In the figures we gave, 80 per cent. of the patients showed objective clinical improvement of 2+ or better, while 95 per cent. showed significant improvement in the synovial fluid.

The degree of response to intra-articular therapy has varied from time to time, probably because of spontaneous variation in the activity of the disease.

In answer to Dr. Jessar we, too, have seen no definite changes in the total protein and albumin/globulin ratios of the synovial fluid.

Following Dr. Key's remarks, we do not use novocaine either; and as regards the suggestion that merely needling a joint may produce improvement, our control results, which were not very good, do take care of that problem.

Evaluation of Hormone Therapy in Rheumatoid Arthritis.

By WALTER BAUER, WILLIAM S. CLARK, MARIAN W. ROPES, and J. PETER KULKA, *Boston, Mass.*

In a series of 48 patients treated with ACTH and/or cortisone for periods of 8 to 680 days, 31 received cortisone alone, nine ACTH alone, and eight cortisone and ACTH in separate courses. Dosages ranged between 12·5 and 300 mg. daily for cortisone and 20 and 280 mg. daily for ACTH. 22 patients received cortisone for longer than 3 months and twelve for longer than one year. Eight received ACTH for longer than 3 months but all were treated less than one year. Cortisone was administered orally and parenterally and ACTH intravenously as well as intramuscularly, using both short and long-acting preparations. The administration of either hormone usually resulted in subjective improvement with less striking objective improvement. Increased agility and functional improvement were the most striking features. Hormone therapy did not result in lasting remissions; in fact in some instances disease progression was observed.

Side-effects included psychoses, acne, hirsutism, obesity, hypertension, oedema, thrombophlebitis, a pathological fracture, diabetes, and infections. The sedimentation rate frequently decreased but usually remained above normal. Electrophoretic observations revealed changes toward normal in the fibrinogen, albumin and alpha- and gamma-globulin. Synovial fluid studies and joint biopsies revealed suppression of inflammation. Metabolic studies indicated no relationship between anti-rheumatic effects and the measurable effects of the adrenal hormone.

Our observations indicate that cortisone and ACTH are primarily effective because they control the stiffness, aching, and pain of rheumatoid arthritis, thereby permitting functional improvement. They cannot be widely applied and should never be solely relied upon in the management of this disease.

DR. BERNARD M. NORCROSS (*Buffalo, N.Y.*): By and large, I agree with these conclusions. I began to use hormone therapy in rheumatoid arthritis with great enthusiasm 2 years ago; to-day I am wiser and more philosophical about it, but I believe there is a definite place for the use of hormones.

I shall restrict my comments to an account of a group of twenty patients, all of whom received ACTH for periods of over a year, some for nearly 2 years. Fourteen patients show various grades of improvement and are still receiving ACTH therapy; two have changed to oral cortisone therapy at their own request to avoid further injections; one became refractory to ACTH and has been maintained on intermittent cortisone therapy; one has continued to improve after therapy was discontinued; and in two therapy was discontinued because of pregnancy. Both the last two patients had a normal pregnancy and delivery of a normal baby; one had the usual remission during pregnancy, but the other required hormones at various times for relief of the arthritic symptoms.

In this group of patients, the reactions were not severe. We had the usual minor side-effects (acne, hirsutism, excessive weight gain), and in one patient osteoporosis and the fracture of a vertebra may have been influenced by hormone therapy. Another patient sustained a hip fracture after minor trauma. Our most serious problem is how to discontinue hormone therapy in the remaining patients and we have, so far, no answer to that question.

One interesting case is that of an 11-year-old child who was malnourished and painfully disabled, and had been a bed patient for almost a year. During 20 months of ACTH therapy, he has grown 4 in. and gained 20 lb., and he has now been maintained in complete clinical remission for over 6 months. But I do not believe we have cured his disease because *x*-rays show some progression of the arthritis and osteoporosis.

In conclusion, I believe this drug may be of value in two groups of patients besides those suggested by Dr. Bauer. The seriously ill juvenile rheumatoid patients and the few chronically disabled adults who can afford and also tolerate it for a prolonged period, will be helped to a considerable degree.

DR. RUSSELL L. CECIL (*New York*): I have no statistics to present, and maybe the audience will heave a sigh of relief over that. Dr. Kammerer and I are now in the midst of a follow-up study of our patients with rheumatoid arthritis who have received cortisone. I have had the impression for some time that there is just about one patient in ten to whom the hormone therapy was really an answer to prayer, and who received 100 per cent. continued relief. I was quite pleased that my rough estimate came so near the actual figures of objective improvement presented by Dr. Bauer. Others derive subjective benefit for a time. I have been particularly interested in the number of side-reactions, and the

number of patients who requested the cortisone be discontinued because its effect was " petering out ".

A patient may be going along on two or three cortisone tablets a day, when he begins to have new symptoms and new joints are affected. Then if he is of only moderate means he will complain that the stuff is not worth the money and decide to stop taking it. The answer may be that we have not given big enough doses, but larger doses have obvious disadvantages. I do not think we are getting really A1 results in more than 10 per cent. of our patients and although I agree that there is a place for these hormones in the treatment of arthritis, I have come to use them with a certain reluctance.

DR. HERMAN H. TILLIS (*Newark, N.J.*): Has anyone had any experience with thrombophlebitic complications? Has Dr. Bauer noted any such changes as the marked increase of blood platelets ? In two of our cases that eventually died we found such an increase; one had a platelet count of 680,000 and the other over 800,000; and we have found very high platelet counts in many other patients on long-term hormonal therapy.

DR. MORTIMER EHRLICH (*New York*): We should like to present an analysis of ninety cases treated with cortisone and ACTH for a period of one year or longer.

Of 41 cases, approximately 40 per cent. of our original number of 90 cases, eight were treated with ACTH, and 26 of these have been on treatment for over one year, and fifteen for 1½-2 years.

Of this group of 41 cases, thirteen are now having partial remissions sufficient to warrant a rest period of 3 to 14 months without exacerbation, and two of these thirteen cases have been in complete remission for periods of more than 3 months. Five patients in this long-term group have presented demonstrable articular damage, despite symptomatic control, but ACTH and cortisone have provided remarkable control of active symptoms. They are potent, rapid, consistent agents, but must still be regarded as requiring of continued study.

DR. ROLAND DAVISON (*San Francisco, Calif.*): Has Dr. Bauer had any experience with patients who become pregnant while taking cortisone ? I have two patients whose pregnancy is fairly advanced. It has been our experience that patients with rheumatoid arthritis go into remission during pregnancy, but both these women have not only not gone into remission but have become progressively worse. They have had increased doses of cortisone, and even attempted pressure control, but continue to get worse.

DR. CHARLES M. PLOTZ (*Brooklyn, N.Y.*): In answer to Dr. Davison, we have one patient who was given cortisone by her physician for the first 7 months of her pregnancy in the mistaken belief she was developing amenorrhea due to the cortisone. She was taken off cortisone in the seventh month and had no relapse at that time. She had a normal delivery of a normal baby but relapsed 2 months after delivery.

CHAIRMAN: Dr. Cecil referred to the beneficial effects of cortisone " petering out " after a month or two. In my presidential address I did not use the words " petering out ". That is a good description of what happens when the patient is permitted to go into the hypercortisone state, and cannot distinguish between the rheumatic complaints of hypercortisonism and a true rheumatoid flare. Many of these patients need less rather than more cortisone. There is so much variation in tolerance of cortisone that individual doses must be estimated for each patient. Most women go into a hypercortisone state on 50 mg. cortisone daily within about two or more months, and many post-menopausal women show hypercortisonism on 37·5 mg. cortisone daily. If a patient shows signs such as rounding of face, abnormal fat pads, hirsutism, acne, etc., a special inquiry must be made regarding their symptoms, including rheumatic complaints such as periods of fatigue, muscular, fibrous and joint aches, and swings of mood. The presence of some synovitis does not necessarily mean that the patient needs more cortisone. To the maximum relief from cortisone short of hypercortisonism should be the aim for long-term therapy of rheumatoid arthritis. Complete control of rheumatic symptoms is not the final criterion of the necessary dosage.

DR. BAUER: As I said before, I do not know whether hormone therapy played any role in the production of the thrombophlebitis in the two cases in our series. In one of them it seems fair to conclude that it *was* a manifestation of the disease because autopsy revealed a widespread vasculitis similar to that seen in several autopsied cases of rheumatoid arthritis who had never received hormone therapy.

I was unaware that cortisone therapy could cause platelet thrombi and thereby thrombophlebitis. Here again we must entertain the possibility that the platelet thrombi are a manifestation of the disease process. I know they can occur in disseminated lupus erythematosus and I presume they may be encountered in other types of widespread vasculitis. There are recorded cases of platelet thrombi which we cannot explain.

I know of only one patient who received cortisone during pregnancy, and in this case there was no demonstrable ill-effect on either mother or infant. In this instance ACTH was administered in the last two weeks of pregnancy during which time the cortisone was discontinued gradually.

Dr. Davison's observation that rheumatoid arthritis is failing to respond during pregnancy is of interest and difficult to explain.

Combination Therapy in the Treatment of Rheumatoid Arthritis. By DWIGHT C. ENSIGN and JOHN W. SIGLER, *Detroit, Mich.*

It is well recognized that any single method of treatment often fails to induce and maintain a worth-while remission in rheumatoid arthritis. Combination therapy appears to be a more useful approach, particularly in refractory cases.

The following therapeutic combinations have been used in a total of nineteen patients:

(1) Cortisone (orally) and gold salts.
(2) Gold salts and intra-articular hydrocortisone.
(3) Cortisone (orally), gold salts, and intra-articular hydrocortisone.

Comprehensive measures (physiotherapy, balanced rest, and exercise, and salicylates) were used.

DR. CORNELIUS H. TRAEGER (*New York*): Our experience of rheumatoid arthritis treated with combined gold and cortisone involved eighteen cases:

(*i*) Gold and cortisone begun simultaneously.
(*ii*) Gold first and cortisone subsequently added.
(*iii*) Cortisone first and gold subsequently added.

Our results revealed that when sufficient gold had been administered to anticipate a beneficial effect from this

treatment alone, the effects of cortisone were nullified and the arthritis activity was resumed. Continuation of both gold and cortisone for several months did not change the results. Thus in eighteen patients, regardless of whether gold or cortisone was administered first or simultaneously, it was possible to demonstrate a mutual antagonism.

In four out of five the cessation of cortisone and subsequent treatment with gold resulted in a control of the arthritic process.

The type of gold compound used, the duration of the arthritic process, and the stage or functional status of the patient before therapy did not influence the results.

In two cases on both gold and cortisone, the increase in cortisone requirements to overcome the antagonistic effect of the gold resulted in gastric haemorrhage.

DR. EDWARD E. ROSENBAUM (*Portland, Oregon*): We have been doing the same as Drs Ensign and Sigler at the University of Oregon Medical School with almost similar results.

For the past 18 months we have treated forty patients with rheumatoid arthritis, using a combination of cortisone and gold salts.

We also used physiotherapy, adequate diets, and rest. At the end of a 3-month period we discontinued cortisone and maintained weekly injections of gold, and in about half of our cases, we were able to maintain the gains made with cortisone by using gold salts only.

Dr. Ensign did not mention toxic reactions. We encountered none from gold while cortisone was being administered, but after the cortisone was discontinued 30 per cent. of our cases developed some symptoms or signs of gold toxicity. We were able to control these toxic reactions by an additional course of cortisone.

I think that it is worth mentioning that an occasional patient can be made worse by combined therapy. Three of our forty patients showed both clinical and objective evidence of increased rheumatic activity.

DR. HARRY E. THOMPSON (*Tucson, Ariz.*): We have been interested in combined cortisone and gold therapy for the last 2½ years, and have studied three groups of patients:

(*i*) Fifteen patients who were receiving gold with only a Grade II to III improvement, were given cortisone in addition. None had any remission.

(*ii*) 29 patients were started on cortisone and gold simultaneously. Of these, nine (31 per cent.) have a Grade I therapeutic response, and have now been on gold and off cortisone for 1 to 1½ years.

(*iii*) A control group was given gold alone, and here the results were the same as or very slightly better than in Group (*ii*). This may be because Group (*ii*) included ten reactors to gold who may therefore have responded to it less a second time.

Nine of these ten who had been reactors to gold tolerated gold with cortisone. The one exception, which is a questionable one, was a patient who was still on his gold and cortisone, when he developed an acute thrombocytopenic purpura.

It appears that the combination of cortisone and gold given simultaneously, is a good one, particularly since cortisone may be used with gold to establish rehabilitative measures before the gold levels became effective, and may be discontinued when the gold takes effect. It seems also that there is less danger of a reaction to gold when it is given with cortisone.

DR. WILLIAM H. KAMMERER (*New York*): At the spring meeting of the New York Rheumatism Association in 1951,[1] we reported the results of combined cortisone and gold therapy in a group of thirty patients.

The original plan was to take those patients who had been on gold for some time, with minor or major improvement, to give cortisone in a short course in an attempt to try to push them into a remission, and then to hold this remission by continuing gold therapy alone.

Later some other patients were started on gold and cortisone simultaneously. With two or three exceptions, this combined therapy seemed to add nothing, and we feel that the physician should decide which of the two methods he wishes to use and then stick to that alone.

DR. JOSEPH L. HOLLANDER (*Philadelphia, Pa*): As Dr. E. M. Brown, Jr., told you (above p. 301), 79 of our patients who received local hydrocortisone were also on gold therapy, and 71 were on systemic cortisone therapy, and seven were on both, along with the Compound F.

We feel that one cannot compare such a series very accurately because only our earlier and milder cases are treated with gold the Compound F being an adjunct. We feel that if cortisone and gold are antagonistic, as some suggested, the least we can say is that local hydrocortisone injections into the worst joints had no such antagonism to gold treatment. Spontaneous remissions, or remissions from gold therapy, do occur with this combination of treatment, and several of our fairly early rheumatoid cases treated with gold and intra-articular "F" have appeared to go into remission.

DR. —. CLARK (*Boston, Mass.*): I should like to comment on the classification of improvement by the American Rheumatism Association criteria.

These data appear to reveal a strikingly better result with combined therapy than that obtained with ACTH or cortisone alone as reported by us. The American Rheumatism Association criteria of improvement lists four classifications. Before a patient's condition can be classified as Grade II improvement, he must have only minimal swelling of his joints, and, in order that transient improvement of the disease may not be misleading, the improvement must be maintained for one year.

This means that if the patient has an exacerbation of the disease or an exacerbation in one joint at any time during the course of a year, he is automatically classified as Grade III or IV.

These criteria were adopted to facilitate interpretation of therapeutic data from different clinics. If they are followed at all, they should be followed to the letter. A liberal interpretation of results by this system makes it difficult to evaluate reports, and if the criteria are not adequate for standardizing the therapeutic effectiveness of an agent, they should be either changed or dropped. I should like to ask Dr. Ensign if he has applied the literal or the liberal interpretation of American Rheumatism Association criteria to his results.

DR. WILLIAM C. KUZELL (*San Francisco, Calif.*): I think that often, when we are using these strong agents, we get away from our fundamental principles of pharmacology. It is a well-known fact that the tolerance of the animal organism to heavy metals can be increased by repeated low dosage. It is also conceivable, but not proved by any animal studies known to me, that cortisone could inhibit this building up of tolerance by the animal organism. Thus, when cortisone is discontinued after a large total dose of gold, severe toxic gold reaction may result.

[1] *Annals of the Rheumatic Diseases* (1951), **10**, 193.

I think this should be kept in mind particularly with aged patients. Cortisone should be continued after the total gold dosage exceeds about 750 mg.

DR. ENSIGN: As far as Dr. Traeger's comment is concerned, we have seen no evidence of any mutual antagonism between these two agents.

I was interested to hear of Dr. Rosenbaum's experience with a larger group of patients. Apparently he feels as we do that these new treatments are only supplemental to the time-tried methods which are, after all, our mainstay. It is only in order to make those measures more effective in a shorter time that we felt justified in carrying out these therapeutic variations.

We have not experienced any toxic reactions in this particular group of patients except for a couple of minor skin rashes which did seem to be better with the cortisone.

I think we should emphasize one point which was hinted at: that the occasional patient can be made worse by any of these drugs that improve his sense of well being and free him from joint pain, so that he damages the diseased joints. Many of our patients have to be carefully watched. We have had our share of patients who have had all kinds of treatment elsewhere before they came to us, including repeated doses of gold salts, and almost everything else you could think of. One thing we have to contend with in Detroit that you do not have elsewhere is red-ant juice which is given by one of our local impressarios. (Laughter.) Some of those patients who are already in a Grade IV stage of the disease are not suitable for this type of therapy, in our judgement.

I should like to stress Dr. Hollander's point: we also use these things merely as adjuncts to the old established forms of therapy.

As far as our interpretation of the Grades of therapeutic response and the other elements in the classification of the American Rheumatism Association, we were not justified in applying those criteria to the last two cases of gold salts plus hydrocortisone and of gold salts, cortisone, and hydrocortisone, because those patients have not yet been followed for a year.

Adrenal Cortex Function in Patients receiving Continuous Long-Term Cortisone Therapy. By E. P. ENGLEMAN, M. KRUPP, HAROLD JOHNSON, J. E. WELSH, and B. M. MEYER, *San Francisco, Calif.*

Adrenal cortex function was studied in eighteen patients who were given cortisone continuously without interruption from 12 to 26 months. In most of these cases, the diagnosis was rheumatoid arthritis. Daily oral doses of cortisone ranged from 37·5 to 100 mg. Criteria for adrenal responsiveness included changes in the eosinophil count and in the urinary 17 ketosteroid and "corticoid" output after intravenous ACTH.

In each patient, adrenocortical function could be shown despite the continued ingestion of cortisone. In contrast to untreated individuals who were tested, it was often necessary to give two to four daily infusions of ACTH before any response could be demonstrated.

Our studies showed that:

(*a*) adrenocortical function was suppressed by long-term administration of "maintenance" doses of cortisone,

(*b*) cortisone-induced suppression of function of the adrenal cortex was reversible, even in patients who received as much as 100 mg. cortisone daily for as long as 22 months.

Discussion.—DR. THEODORE B. BAYLES (*Boston, Mass.*): We have been using two large doses of cortisone. It is interesting to see what the adrenal cortex will do without stimulation.

First it was given without any stimulation and stopping abruptly (500 mg. cortisone daily for from 14 to 30 days). It was given orally and parenterally, and within 7 days the eosinophil count returned to normal in all but one of the patients who had the large dose by mouth. Within 3 weeks all but one, without any stimulation, returned to a normal eosinophil count after the cessation of parenteral therapy.

Secondly we have those receiving a weekly 4-hour ACTH test, and here again those receiving cortisone by mouth returned to normal more rapidly without stimulation. All but one of the oral cases were back to normal within 10 days responding to a simple 25 mg. ACTH 4-hour test, and, except for a rare example, most of the parenteral cases were back within 3 weeks, with a simple weekly ACTH test, and no massive stimulation.

DR. J. ALBERT KEY (*St. Louis, Mo.*): Dr. Bayles is much braver than I when it comes to the sudden withdrawal of large doses of cortisone.

Natural Course of Cushing's Syndrome as compared with the Course of Rheumatoid Arthritis treated by Hormones. By CHARLES M. PLOTZ, ABBIE I. KNOWLTON, and CHARLES RAGAN, *New York.*

The present trend towards long-term therapy with cortisone and ACTH for a variety of disease entities has given rise to some concern for the physiological hazards of these hormones. With this in mind, a group of 222 cases of naturally occurring hyperadrenalism, or Cushing's syndrome, have been analysed. 33 cases from the Columbia-Presbyterian Medical Centre have been followed in detail, and all but one are known to date or until death. 114 autopsied cases are considered.

The natural history of Cushing's syndrome is discussed in detail. It is emphasized that this is largely a clinical diagnosis with varying aetiologies all of which produce hyperadrenocorticalism. The leading causes of death were infection, complications of cardiovascular disease, and neoplastic disease.

In a preliminary fashion, a group of 100 patients treated with cortisone or ACTH for an average of 15 months is considered. While this group has as a whole exhibited all of the major manifestations of natural Cushing's syndrome, the incidence of symptoms and signs is generally much lower and their severity not so striking. The incidence of peptic ulcer in the iatrogenic cases of hyperadrenalism is not duplicated in the naturally occurring disease.

Discussion.—DR. WILLIAM Q. WOLFSON (*Ann Arbor, Mich.*): This paper differentiates the dangerous Cushing's syndrome from the much milder induced therapeutic hypercorticoidism usually seen during long-term ACTH or cortisone administration. A relative freedom from undesirable physiological disturbance is frequently seen. Two of our patients, one with rheumatoid arthritis and one with disseminated lupus erythematosus, each received full suppressive doses of ACTH continuously for more than 3 years, but neither patient has any clear-cut physical manifestation of hypercorticoidism,

only one has laboratory evidence of corticogenic hypothyroidism, and both have regular normal menses with cyclic ovulation. In one case evidence of this last is derived from the basal temperature curve, but in the other patient pregnancy has only last month provided unequivocal proof of relatively normal pituitary-gonad relationships. In contrast, a diagnosis of Cushing's syndrome is generally considered untenable in the presence of normal cyclic menstrual function.

A second difference between spontaneous Cushing's syndrome and therapeutic hypercorticoidism is the presence of a continuous eosinopenia in the spontaneous endocrinopathy. At any time during the day, the patient with Cushing's syndrome generally has an eosinophil count of less than 50 cells per c.mm. In the patient receiving single daily doses of long-acting ACTH, equally low counts are usually seen only from the 6th to the 16th hour after the dose is given and not always then; with divided daily doses of oral cortisone counts may be continuously well above 50 per c.mm. despite good therapy. The simplest explanation of this finding is the assumption that the increase in circulating corticoid of the Compound F type is much greater in spontaneous Cushing's syndrome than during therapeutic hypercorticoidism.

A third difference is less easily explained. An appreciable minority, perhaps 10 per cent., of patients with Cushing's syndrome show mild polycythaemia vera which is otherwise indistinguishable from primary polycythaemia vera. We have been watching for reports of the development of polycythaemia during long-term ACTH or cortisone administration, but, to the best of our knowledge, no such instance has yet been reported. Does this mean that a qualitative, as well as a quantitative change in adrenal function occurs in spontaneous Cushing's syndrome ? It is certainly difficult to explain the low 17-ketosteroid output of some of the Cushing patients who are supposed to be secreting large amounts of Compound F, a relatively good 17-ketosteroid precursor.

DR. WALTER BAUER (*Boston, Mass.*): I think we owe a vote of gratitude to the Presbyterian group. They have sounded a warning, and I think we should all take it with much more than a grain of salt.

DR. PLOTZ: As far as polycythaemia is concerned, in our large series of cases with Cushing's syndrome, this was a most inconstant finding, and occurred in only about one-third of the patients; in other words, about two-thirds of the patients with Cushing's syndrome did not manifest any degree of polycythaemia.

The eosinophil response, of course, may be a function of the continuous stimulation of Cushing's syndrome as opposed to intermittent stimulation.

N,N' Dibenzylethylenediamine Dipenicillin G (Dibenzyl Penicillin), as a Prophylactic and Therapeutic Agent against Group A Streptococci. By GENE H. STOLLERMAN and JEROME H. RUSOFF, *New York*.

N,N' Dibenzylethylenediamine Dipenicillin G (Dibenzyl penicillin), a new repository type of penicillin, was administered to a group of 125 children, aged 6 to 14, convalescing from rheumatic fever, to determine its possible value as a prophylactic and therapeutic agent against group A streptococci.

Detectable serum levels of penicillin were found for unusually long periods following single intramuscular injections. A continuous penicillin serum level was maintained in patients receiving 300,000 units intramuscularly once weekly and in those receiving 600,000 units once every 2 weeks. When 1·2 million units was administered, detectable penicillin serum levels were found in 90 per cent. of patients 3 weeks later and in 67 per cent. at the end of a month.

The carrier state was eliminated in all of five patients in whom Group A streptococci had previously been found by throat culture. Weekly throat cultures were negative for group A streptococci in all treated patients during the 7-month period of study. There were no recurrences of rheumatic fever in the treated group. There was no significant change in the pharyngeal flora at the end of 3 and 6 months.

Reactions were limited to transient local pain and tenderness at the site of injection and, in two patients, mild urticaria which lasted about 48 hrs. and did not recur when injections were continued.

Discussion.—DR. CHARLES H. RAMMELKAMP, JR. (*Cleveland, Ohio*): These results are very important, primarily, as Dr. Stollerman emphasized, for the prevention of rheumatic fever as well as for controlling streptococcal outbreaks in large population groups.

There are, however, certain aspects that I do not quite understand, and I should like to ask Dr. Stollerman how Dipenicillin is excreted. It is hard to understand how 600,000 units remain in the body for one month unless it is not only insoluble, but is also not excreted through the kidney in the active form. Is there any evidence of how it is excreted ? What are the clearance rates of this substance through the kidney ?

DR. CURRIER MCEWEN (*New York*): I should like to emphasize that the great difficulty with our present methods of prophylaxis in rheumatic fever is the human factor. Whether one uses sulfa-diazine or oral penicillin, success is dependent on the regularity with which the patient takes the medication. All too often haemolytic streptococcal infections which result in rheumatic fever break through in spite of the usual prophylactic measures; and how frequently, on follow-up of the patient, one finds that the prophylactic regimen has not been followed.

The measures are good. It is the patient and the patient's family that are the weak links. Therefore a modification like that reported by Dr. Stollerman which can largely remove the need to rely on the patient's memory and cooperation holds out great promise.

DR. STOLLERMAN: In answer to Dr. Rammelkamp, we have not yet performed any studies on the excretion of this compound. Like him, we were also sceptical at first that the dose injected could persist for such long periods. We have, therefore, performed the following theoretical calculation: If the adult renal plasma flow averages 700 ml. per min. and the average penicillin plasma concentration is 0·04 units of penicillin per ml., a patient would excrete 40,000 units of penicillin per day, assuming that penicillin is completely cleared at this concentration (this is a reasonable assumption at such low penicillin levels). Thus, if a patient excretes 40,000 units of penicillin per day after an injection of 1·25 million units of bicillin, penicillin could remain in the body for 31 days. This, of course, is only a theoretical calculation.

In answer to Dr. McEwen, our interest in this compound originated in our discouragement at the failure of patients to conform to the prophylactic regimen of daily oral doses of penicillin or sulfonamides.

Significance of Hepatomegaly in Children with Rheumatic Fever receiving Adrenal Cortical Hormone Therapy. By JANET S. BALDWIN and JEROME H. RUSOFF, *New York*.

Enlargement of the liver has been observed in a number of children during hormone therapy for active rheumatic fever. In some instances, although there was evidence of active carditis, the total clinical findings did not indicate congestive failure as the cause for the hepatomegaly. In other instances there was no evidence of carditis either by clinical or laboratory observations.

Liver enlargement usually begins fairly soon after starting therapy and regresses more slowly on withdrawal of hormone therapy.

There was an opportunity of studying one such case by needle liver biopsy at the height of liver enlargement and after recession in size 3 weeks later. Marked fatty infiltration present in the first section had regressed strikingly in the later biopsy sections.

The recognition and evaluation of hepatomegaly as due to factors other than congestive failure are particularly important in the management of hormone therapy in active rheumatic fever.

Histochemical and Electrochemical Approaches to the Problem of Connective Tissue Composition. By H. R. CATCHPOLE, *Chicago, Ill.* (by invitation).

Two aspects were discussed: the chemical composition of connective tissue as shown histochemically, and the physical state of these components, as inferred histo- and electrochemically. For the first, the Hotchkiss-McManus method for the staining of glycoprotein entities has been combined with freezing-drying fixation and the use of various solvents and enzymes to study the distribution of glycoproteins in tissues, and their relative solubility in different tissue states. Thus, changes in the solubility of ground substance and basement membrane were detected in wound healing, ageing, experimental oedema growing tumours, stimulated ovary, relaxing symphysis, and other conditions. It was further found that the intravital dye, Evans blue, which normally fails to stain connective tissue, is taken up by modified connective tissue, and can be demonstrated after freezing-drying in those sites which show altered solubility.

Electrochemical studies in progress with Drs N. R. Joseph and M. B. Engel have employed the pubic symphyseal connective tissue of guinea-pigs, a tissue which under hormonal stimulation "relaxes" from a tight, relatively immovable state, to a loose, flexible one. During this process, diffusion potentials with respect to a perfusing solution of one-tenth isotonic NaCl change progressively from high positive potentials (20—30 mv.) to negative values (—5 to —10 mv.) characteristic of aqueous junctions. This is interpreted to mean that the following events take place:

(1) a breakdown of negatively charged polysaccharide-containing macromolecules to smaller entities,

(2) bringing in of water and electrolyte to give tissue hydration,

(3) physical changes corresponding to these processes, such as increase in bulk and decrease in strength or resistance of the tissue.

Studies using other perfusing ions, such as K, Li, Mg, Ca, have shown a specific immobilization of K in "tight" connective tissue, with progressive mobilization as the tissue loosens. These potentials depend on the presence in tissues of negatively charged colloidal aggregates whose density may be estimated from the magnitude of the potentials. Experiments with other variable connective tissues, such as skin and avian comb, and the correlation of potential findings with histochemical appearance, were described.

Influence of Primaquine on the Clinical Findings and Joint Potentials in Rheumatoid Arthritis. By IRVING E. STECK, SIMON ZIVIN, NORMAN JOSEPH, and MAX M. MONTGOMERY, *Chicago, Ill.*

A series of 21 patients with rheumatoid arthritis was hospitalized for treatment with primaquine, an antimalarial 8 aminoquinoline drug. During the hospitalization the clinical and laboratory effects of this drug were observed and frequent electrical potentials of the synovia of the knees were obtained. After a control period of one or more weeks, the drug was administered for 14 days, followed by a second period of observation for one or more weeks. The electrical responses were compared with those obtained with ACTH or cortisone given under similar conditions.

Beneficial effects were observed in all patients and in two cases a complete remission was induced. Eight cases sustained a prolonged partial remission from 1 to 10 months. Six cases relapsed to their former state within 1 to 3 weeks after cessation of primaquine administration. In five cases follow-up was not possible.

The side-effects were frequent, consisting chiefly of methaemoglobinaemia and pallor in all cases, anorexia in 66 per cent. and leucopenia in 33 per cent. None of the side-effects was permanent.

The electrical potentials showed a definite drop. The electrical responses developed more slowly and were not as steep as those obtained with ACTH and cortisone. The maximum drop occurred between the fifth and tenth days, whereas with the steroids the fall occurred on the first and second days. However, the electrical potentials returned to about the same level on the twelfth to fifteenth days in the primaquine, ACTH, and cortisone groups.

Discussion.—COL. RALPH M. PATTERSON, Medical Corps (*Army-Navy Hospital, Hot Springs, Arkansas*) Our study with primaquine in rheumatoid arthritis was instigated by Dr. Alving of the University of Chicago, and carried out in cooperation with him. Our findings are similar to those described by Dr. Steck.

The investigation was set up to include for statistical evaluation:

(1) a complete history and physical examination;

(2) complete roentgenologic evaluation;

(3) arthritic profile by the investigation board prior to, immediately following and several weeks following the treatment;

(4) photographic studies, both with motion and still pictures to demonstrate joint involvement and range of motion as seen prior to and subsequent to treatment;

(5) electrocardiographic studies done every two days during treatment on the initial series;

(6) weights and heights recorded at weekly intervals;
(7) daily personal diary of the patient;
(8) numerous laboratory procedures, including methaemoglobin levels three times weekly, complete blood and platelet counts, sedimentation rates, blood calcium and phosphorus, serum protein, and albumin/globulin ratio, and blood sugar each week, blood sodium and potassium, urinary 17-ketosteroids, urinary uric acid, and creatinine excretions every 3 days.

Throughout the investigation period all the patients studied, both controls and drug cases, were continued on a basic regimen of physical therapy which had in most cases been instituted some time before.

All patients in the initial treatment group were given 10 mg. primaquine every 4 hours for 14 days.

Several patients treated later were given varying doses over variable periods of time. All the controls were given placebo lactose tablets of identical size and colour every 4 hours for 14 days.

All patients in the group had rheumatoid arthritis, except one with severe dermatomyositis, one with disseminated lupus erythematosus, and one with osteoarthritis and fibrositis.

Of the 63 patients with rheumatoid arthritis, 35 had involvement of the peripheral joints alone (Table I), nineteen combined peripheral joint involvement and spondylitis (Table II), and nine spondylitis alone (Table III).

Definite objective improvement was demonstrable within 3 weeks in 57·1 per cent. of the peripheral joint group, in 21 per cent. of the combined group, and in none of the spondylitic group (Table IV).

Nineteen patients were treated with placebos for 2 weeks, and subsequently with primaquine for 2 weeks (Table V). Of this group, objective improvement was noted in 10·5 per cent. during the first 2 weeks and in 50 per cent. during the second 2 weeks, one patient having been dropped from the study group. This 40 per cent. on the credit side within a 2-week period is thought to be of clinical significance. The toxic manifestations seen were much the same as described by Dr. Steck. Methaemoglobinaemia occurred in all cases, but only two patients had to be treated for it. Abdominal distress was common. Leucopenia occurred in only two patients in the latter group treated over a prolonged period of time. Bradycardia occurred in one case.

We feel that primaquine exerts some anti-rheumatic effect and is helpful in certain cases of rheumatoid

TABLE I

RESPONSE TO PRIMAQUINE IN 35 CASES OF PERIPHERAL RHEUMATOID ARTHRITIS

Case No.	Age (yrs)	Duration	Grade of Severity	Previous Special Therapy	Improvement		Comment
					Subjective (%)	Objective (Grade)	
2	52	4 mths	3	None	75	3	—
3	53	4 yrs	3	Gold	0	nil	Left hospital 1 Sept., 1950; no follow-up
4	24	3 mths	2	None	30	3	—
7	24	15 mths	2	None	0	nil	—
8	21	10 mths	1	None	0	nil	—
9	26	4 mths	2	None	90	4	Remission
11	21	5 mths	3	None	75	3	—
12	30	6 yrs	3	None	50	2	Flare-up 2 mths later; re-treated.
13	18	6 mths	2	None	0	nil	—
14	27	5 yrs	4	Gold Testosterone	50	2	—
15	28	9 mths	1	None	50	2	—
17	28	4 yrs	3	None	90	3	Near remission
18	21	8 mths	1	None	0	nil	Remission in August on placebo—flare-up 2 mths later; unaffected by re-treatment
21	38	14 mths	1	None	0	nil	—
23	34	18 mths	4	None	80	3	Near remission
26	29	15 mths	2	None	50	2	Has completed three courses
27	19	12 mths	2	Testosterone Pregnenolone	0	nil	—
29	20	9 mths	2	None	0	nil	—
39	37	7 yrs	2	None	50	2	Syphilis treated while on primaquine
40	49	30 mths	3	ACTH	0	nil	—
41	48	12 mths	3	None	75	3	—
46	17	5 mths	3	None	50	2	—
48	42	33 mths	4	None	10	nil	—
52	35	36 mths	3	None	10	nil	—
53	31	4 mths	1	None	100	4	In remission
(1)	37	5 yrs	3	None	50	2	60 mg. 1 wk; 75 mg. 1 wk. Mild leucopenia
(4)	19	6 mths	2	None	0	nil	Improved on chrysotherapy 90 mg. 14 days
(8)	26	5 yrs	3	None	90	3	Two courses of 2 wks each
(10)	21	3 mths	4	None	90	3	60 mg. for 25 days; no other treatment
(11)	22	8 mths	4	Testosterone	0	nil	60 mg. 6 wks
(12)	25	2 mths	3	Typhoid vaccine	50	3	60 mg. 3 wks
(13)	5	6 wks	3	ACTH-Cortisone	0	nil	5 mg. × 4
(14)	33	3 mths	4	None	50	nil	90 mg. 22 days
(15)	62	4 mths	4	Cortisone	75	3	30 mg. 57 days. Leucopenia
(16)	42	5 mths	2	None	50	2	3·9 methaemoglobin

TABLE II

RESULTS IN NINETEEN CASES OF COMBINED PERIPHERAL AND SPINAL INVOLVEMENT

Case No.	Age (yrs)	Duration	Grade of Severity		Previous Special Therapy	Improvement		Comment
			Peripheral	Spinal		Subjective (%)	Objective (Grade)	
1	22	9 mths	1	1	None	75	3	—
16	32	24 mths	2	1	None	0	nil	—
19	33	10 mths	1	3	None	10	1	—
20	28	10 mths	1	1	None	75	2	Flare-up 2 mths later; re-treated
32	30	7 yrs	3	4	Pregnenolone Typhoid	25	2	—
33	22	30 mths	2	1	Radiation	0	1	—
34	19	5 yrs	1	1	None	0	nil	60 per cent. subjective improvement for 2 wks after drug—then flare-up
35	51	7 yrs	4	4	Cortisone	0	nil	—
36	25	6 yrs	2	3	Radiation	10	nil	—
37	31	12 yrs	2	2	Radiation	0	nil	—
44	38	15 mths	1	3	None	0	nil	—
45	30	15 mths	1	1	Radiation	25	1	Hip improvement only
47	27	5 mths	4	1	None	75	2	—
51	20	4 yrs	4	4	Radiation Pregnenolone	0	nil	—
2	22	7 mths	4	2	Typhoid	0	nil	—
3	31	3 mths	4	3	Cortisone	0	nil	Severe nausea and vomiting; drug discontinued after 7 days
5	34	20 yrs	3	2	Typhoid	0	nil	—
6	20	5 mths	3	2	Cortisone (no improvement)	75	3	90 mg. 21 days. 30 mg. 7 days
7	32	3 mths	2	3	Radiation	50	1	Also had malaria

TABLE III

RESULTS IN NINE CASES OF RHEUMATOID SPONDYLITIS

Case No.	Age (yrs)	Duration	Grade of Severity	Previous Special Therapy	Improvement		Comment
					Subjective (%)	Objective (Grade)	
5	25	24 mths	2	None	0	nil	Grade 3 improvement during first course; relapse off drug and no response to second course
10	28	12 mths	4	None	10	1	—
22	42	15 yrs	4	Radiation	30	1	—
28	32	30 mths	4	None	0	nil	—
30	20	6 mths	3	None	0	nil	—
38	33	12 mths	4	None	40	1	—
42	44	14 yrs	4	None	0	nil	—
43	31	6 yrs	4	None	0	nil	—
49	33	24 mths	4	None	5	1	—

TABLE IV

OBJECTIVE RESULTS OF TREATMENT WITH PRIMAQUINE

Type of Disease	Number of Cases	Grade of Improvement					Results (Percentage)	
		4	3	2	1	nil	(4, 3, 2) Improved	(1, nil) Failures
Peripheral	35	2	10	8	0	15	57·1	42·9
Combined	19	0	2	3	4	10	21	79
Spondylitis	9	0	0	0	4	5	0	100
Total	63	2	12	11	8	30	(25) 39·6	(38) 60·4

arthritis, although the mechanism through which it works is not definitely known. It is a toxic drug, however, and must be used with considerable caution.

DR. OTTO STEINBROCKER (*New York*): I hope the remarks on our experience with primaquine do not discourage the authors. They have done a very thorough study and I am merely asking about a minor point.

This material was submitted to us by a manufacturer some time ago for study in our blindfold therapeutic set-up. We usually start with a small group of six or eight; if there is a response of 25 per cent. or more we make a trial with a statistically adequate series.

TABLE V

COMPARATIVE RESULTS OF PLACEBO AND PRIMAQUINE ADMINISTRATION

Type of Disease	Case No.	Degrees of Improvement			
		Placebo		Primaquine	
		Subjective (%)	Objective (Grade)	Subjective (%)	Objective (Grade)
Peripheral	11	0	nil	75	3
	12	10	nil	50	2
	13	0	nil	0	nil
	14	0	nil	30	2
	15	0	nil	50	2
	17	10	nil	90	3
	18	90	3	0	nil
	21	0	nil	0	nil
	23	0	nil	80	3
	26	0	nil	50	2
	27	0	nil	0	nil
	29	0	nil	0	nil
Spondylitis	16	90	4	—	—
	22	0	nil	30	1
	28	0	nil	0	nil
	30	0	nil	0	nil
Combined	19	0	nil	10	1
	20	0	nil	75	2
	32	0	nil	25	2

When we analysed our primaquine group of six patients, two had dropped out, and the other four had each received one 27-mg. tablet four times daily.

We did not give quite the dosage that the authors mention, but it was a little more than the manufacturers had recommended, and that for 4 instead of 2 weeks.

We found that in all four of the patients who had continued there was no subjective or objective response, and no effect on the laboratory data studied. The lack of result may be due to the dosage; I should be curious to know what Dr. Steck says about that.

DR. STECK: We have had no experience beyond the 14-day period of primaquine administration. We were primarily concerned with the effects of this drug on the electrical potentials and were less concerned with its clinical effect, but we shall look into the matter a little more.

Studies on the Metabolic and Antirheumatic Effects of Corticosterone (Compound B). By WILLIAM D. ROBINSON, WILLIAM Q. WOLFSON, and IVAN F. DUFF, *Ann Arbor, Mich.*

The adrenal steroids with definite antirheumatic action, cortisone and Compound F, have manifold effects on organic metabolism; several steroids which affect only electrolyte metabolism have no significant anti-rheumatic action. Cortisosterone has been shown to affect organic metabolism to a degree comparable to cortisone and Compound F. Corticosterone, in a dosage of 200 mg. daily for 10 days, failed to produce clinical or laboratory improvement in a patient with rheumatoid arthritis, although definite changes in both electrolyte and organic metabolism were induced, particularly increases in urinary urate and histidine excretion. The patient subsequently responded promptly to cortisone in doses of 100 mg. daily. Increased urinary excretion of histidine, without other metabolic changes, was also seen during oral and parenteral administration of 11-keto-progesterone; this steroid, a theoretical precursor of corticosterone, had no discernible antirheumatic effect. Such observations suggest that the anti-rheumatic action of cortisone and Compound F is not dependent on gross changes in organic metabolism.

Discussion.—DR. W. PAUL HOLBROOK (*Tucson, Ariz.*): Dr. Robinson has shown in metabolic studies with Compound B nearly all the findings seen with cortisone except clinical remission. We do not yet know how to measure the remission factor or factor X in the laboratory.

As most of you know, we have been studying amino-acids for a number of years and have described what we have chosen to call the remission pattern of amino acids. In this remission pattern there have been extremely high histidine and threonine and moderately elevated lysine and tyrosine urinary excretions. We have so far not seen this pattern of urinary excretion except in the presence of remission. The other amino acids have shown relatively flat curves, except for minor variations.

Dr. Robinson's group was good enough to send us the urine specimens from the patient he has now described, and we have some additional information to offer regarding the amino acid pattern in this particular patient. At peak levels the urinary excretion of histidine on Compound B showed a 300 per cent. increase, and that of threonine a 250 per cent. increase. So far this is a very startling and curious pattern and identical with that we have described as the remission pattern.

The rest of the story is quite different, however, from the remission pattern which we have described. Lysine showed a 150 per cent. increase; serine, 110 per cent.; phenylalanine[1], 400 per cent.; tryptophane, 325 per cent.; tyrosine, 100 per cent.; arginine, 100 per cent. These are rough figures but you can see that this substance Compound B has a very profound influence upon the amino acid metabolism and involves nearly all of them in a dramatic fashion.

I have no explanation for this nor have I any idea

[1] Phenylalanine incidentally has been totally flat in our remission curves.

why this pattern differs from those which we have described, unless it is because the fact that the patient did not experience a remission.

Articular Reactions associated with Localized Fibrous Mesothelioma of the Pleura. By HOWARD F. POLLEY, O. THERON CLAGETT (by invitation), JOHN R. MCDONALD (by invitation), and HERBERT W. SCHMIDT (by invitation), *Rochester, Minn.*

Localized, fibrous mesotheliomata of the pleura have been surgically removed from fourteen men and ten women. These patients ranged in age from 21 to 70 years (average 49·3) and symptoms had been present for from 4 months to 16 years.

Eighteen of the 24 patients had symptoms or findings or both referable to the joints. In many of these such symptoms were the chief complaint, the intrathoracic tumour being discovered in the course of the examination.

Pulmonary osteo-arthropathy (ten cases) was usually accompanied by dependent oedema (six cases). Nine of the ten patients not only had pulmonary osteo-arthropathy but also had articular symptoms and findings similar to those encountered in rheumatoid arthritis. Four other patients had periarticular limitation of a shoulder, while in another three patients the rheumatism was unrelated or only questionably related to the intrathoracic lesion. After pneumonectomy one patient developed peri-arthritis of a shoulder on the same side as the tumour.

Pulmonary osteo-arthropathy and the other articular manifestations related to the presence of the tumour subsided after its removal but recurred with recurrence of the tumour in three out of four cases.

Localized fibrous mesothelioma of the pleura should be suspected when pulmonary osteo-arthropathy is associated with articular symptoms and should be excluded in other cases in which symptoms and findings simulate early rheumatoid arthritis.

DR. RICHARD H. FREYBERG (*New York*): I wonder if Dr. Polley has noted any relationship in the occurrence or the severity of the arthritis to the size of the tumour.

DR. CHARLES L. SHORT (*Boston, Mass.*): I should like to ask Dr. Polley if any periosteal changes were observed in *x*-rays of the long bones of the extremities of these patients, such as are commonly found in the ordinary type of pulmonary osteo-arthropathy. It seemed to me that this condition probably represents a syndrome similar to what we see with carcinoma of the bronchus and other more malignant types of pulmonary tumour.

DR. WALLACE GRAHAM (*Toronto, Ont., Canada*): We have recently observed two patients somewhat like those described by Dr. Polley. The first appeared to have classical rheumatoid arthritis with changes in the fingers, wrists, and knees, but during therapy he developed clubbing of the fingers and investigation revealed a bronchogenic carcinoma. The second patient had congenital heart disease with clubbing of the fingers and toes, and effusion in both knees. In both patients *x*-rays of the knees failed to reveal the periosteal changes described in pulmonary osteo-arthropathy.

DR. THEODORE B. BAYLES (*Boston, Mass.*): Dr. Polley mentioned that these tumours were evident in routine films in eight cases. I wonder how the others were discovered or how he made this diagnosis.

DR. CURRIER MCEWEN (*New York*): I should like to ask Dr. Polley if he has any slides illustrating the clinical appearance of such patients.

DR. POLLEY: Dr. Freyberg's question is intriguing, but in this series the size of the tumour was not correlated with the severity of the articular manifestations. Roentgenograms of the chest seen showed two of the smaller tumours which weighed from 140 to 220 g. The tumours of six of our 24 patients weighed between 4,972 and 1,260 g., those of two between 860 and 825 g., those of eight between 220 and 130 g., and the remainder less than 100 g. The tumours were found in any part of the thorax; they arose from visceral pleura in eighteen patients and from parietal pleura in six. Two of the latter group apparently arose from mediastinal pleura.

In answer to Dr. Short, the periosteal proliferation which is characteristically noted in the roentgenograms of patients with pulmonary osteo-arthropathy was present in the roentgenograms of those patients in this series who had osteo-arthropathy with pleural mesothelioma. This finding was indistinguishable from that observed in patients with other types of pulmonary tumours or even with non-pulmonary diseases in which osteo-arthropathy might occur.

With increasing recognition of the various intrathoracic tumours that may be encountered and of the importance of hypertrophic osteo-arthropathy, it may be possible to determine more specifically the incidence of osteo-arthropathy in association with various tumours. Our preliminary observations suggest, for example, that pulmonary osteo-arthropathy may be much less commonly encountered in cases of bronchogenic carcinoma than in cases of pleural mesothelioma. It should be re-emphasized, however, that pleural mesothelioma is only one type of intrathoracic tumour in which pulmonary osteo-arthropathy may be encountered. Furthermore, as Dr. Graham said, osteo-arthropathy may also occur in other types of pulmonary disease as well as in diseases other than those of the pulmonary tissues. The great frequency of osteo-arthropathy and of certain articular reactions indistinguishable clinically from rheumatoid arthritis in patients with pleural mesothelioma makes this tumour a particularly interesting aspect of the larger problem.

In reply to Dr. Bayles's question about the incidence of abnormal findings in roentgenograms of the thorax, in all the cases in our series an abnormal shadow was noted. In some instances the roentgenogram was taken because of symptoms referable to the respiratory system, but in others the shadow was discovered only in the course of a routine examination of the chest. Special roentgenograms such as lateral views, and views made on use of the Bucky diaphragm, and on expiration as well as inspiration, may be needed in some instances if early evidence of pulmonary disease is to be detected in cases of osteo-arthropathy. A high index of suspicion for a pulmonary lesion (or other disease) is needed when patients have pulmonary osteo-arthropathy.

In answer to Dr. McEwen's question, photographs of the synovial reaction are indistinguishable from the photographs of these abnormalities in rheumatoid arthritis with which you are all familiar. Likewise, the osteo-arthropathy appears exactly like the osteo-arthropathy of other disease.

Plastic Replacement of the Femoral Head for Severe Osteo-Arthritis of the Hip. By JOHN G. KUHNS, THEODORE A. POTTER, WILLIAM A. ELLISTON, and ROBERT S. HORMELL, *Boston, Mass.*

The pain and disability accompanying osteo-arthritis frequently cannot be relieved by conservative measures. Arthrodesis relieves pain, but leaves the patient with severe disability. The conventional type of arthroplasty often fails to benefit much either the pain or disability. Neurectomy leads to lessening of pain, but to no improvement in disability.

In severe osteo-arthritis, there is always severe deformity of the head with version and varus deformity of the femoral neck. This, unless corrected, leads to faulty mechanical action of the hip joint. In order to obtain normal mechanical use of the hip joint, the deformed head must be reshaped or replaced, the acetabulum must fit the head properly and the femoral neck must be reshaped or replaced to approach the normal angulation and directional slant. Acrylic prostheses are moulded to fit each case. These are attached at the proper angulation to the femoral neck. The operation is carried out through a posterior incision which is simple, rapid, and non-shocking. This procedure has been performed in forty patients with severe osteo-arthritis and all are free from pain, 75 per cent. having good function according to the criteria of Judet and D'Aubigné.

Discussion.—DR. EDWARD SCULL (*New York*): What is the relation of the post-operative care to the extensive rehabilitation activities?

DR. WALLACE GRAHAM (*Toronto, Ont., Canada*): The results which Dr. Kuhns has reported are, I think, more favourable than we have obtained after neurectomy. I wonder if he would give us more details about the type of operation which he performs?

DR. KUHNS: In answer to Dr. Scull's question, all of those graded as excellent or good are back at work, and walking about quite easily.

The post-operative care is as follows: The patient is kept in bed usually for about 3 weeks, depending upon how firm the bone of the femoral neck is. He is given exercises, usually after the first few days, but we do not get patients up until the external wound is solidly healed, usually in about 3 weeks. Then he bears only a little weight, walking with the walker or two crutches, and the weight bearing is gradually increased. The patient is walking about sometimes without support in 2 months, but it takes about 6 months to develop strength again in the gluteal muscles.

Dr. Graham asked about neurectomy. I thought someone would ask me about that because there is great controversy as to whether neurectomy is any good or not. I did not say it was ideal. We have found that the only way we can make it helpful is to go into the pelvis and get all of the branches of the obturator nerve, the accessory obturator; and then to turn the patient over and get all of the branches which go to the external rotators of the hip. Then we have done a fairly good denervation of the capsule of the hip.

None of these patients are completely relieved of pain but practically all have some relief, and many say that they are satisfied. But where there is severe distortion of the femoral head, femoral neck, and acetabulum, denervation does not alter the patient's mobility.

Dr. Hartung asked about leg shortening. We have corrected this in a few patients who had deformity of the hip with shortening from youth with a slipped upper femoral epiphysis or displacement of the acetabulum, or congenital dislocation of the hip. By putting on the prosthesis, we have increased the length, and in none has there been any measurable shortening of the leg.

Cortisone in the Treatment of Malum Coxae Senilis. By WILLIAM F. DOWDELL, WALTER M. SOLOMON, ROBERT M. STECHER, and RALPH WOLPAW, *Cleveland, Ohio.*

The dramatic effects of cortisone in rheumatoid arthritis suggested the investigation of its use in malum coxae senilis. Ten patients were selected with definite clinical and roentgenographic evidence of the disease. Each patient served as his own control during the first half of the study during which time a liquid placebo preparation was administered for 22 days. Following the placebo period, a liquid cortisone preparation was administered to each patient for 22 days. Cortisone dosage consisted of 300 mg. the first day in divided doses every 6 hours, 200 mg. the second day, and 100 mg. thereafter for an additional 20 days. Objective observations including, measurements of joint mobility as well as subjective responses were noted at weekly intervals.

Subjective improvement was noted in six of the ten patients while receiving the placebo as compared with subjective improvement in eight while receiving cortisone. Subjective improvement was usually of greater degree in the cortisone-treated patients but not equal to that seen in cases of rheumatoid arthritis treated with cortisone. Increases in joint mobility noted in the ten patients during both the placebo and cortisone treatment periods were for practical purposes equal. All increases in joint mobility noted during the cortisone treatment period were considered clinically insignificant and of a degree not infrequently seen to occur spontaneously in this disease. It was concluded, therefore, that the routine use of cortisone in malum coxae senilis could not be recommended.

Discussion.—DR. MORTIMER EHRLICH (*New York*): We treated fourteen cases of degenerative disease of the hip with cortisone. All were hospitalized for a period of observation and careful control with the use of placebos. Two have now been maintained, with interruption for placebo trial, for more than one year.

Eight had appreciable analgesic benefits in addition to improvement in coordinated functions, and coordinated motion. The remaining six had only moderate relief of pain.

Where there was some joint space left, there was some improvement in joint function.

In this older age group, where cortisone therapy is a measured therapy, you cannot use it routinely. It should be used in cases where the only alternative for the relief of pain might be surgery.

DR. J. ALBERT KEY (*St. Louis, Mo.*): The important thing about a hip is not movement, but freedom from pain and disability and ability to bear weight. The prostheses which are now being widely used, and of

which there are several different kinds on the market, seem to be more effective than the cups.

The important thing is whether the patient has a better hip or not.

Frequently, they have been through so much by the time you get them up that they are willing to settle for almost anything. I have been operating on arthritic hips for a good many years, and I have been very dissatisfied with the results of surgery.

The most important single factor in connective treatment of such cases is rest. Give them a walking cane and make them cut down their activities, and not only does their pain lessen but their movement increases, sometimes to a surprising degree. The best results are obtained with the prosthesis in those hypertrophic or degenerative hips that are operated on early, and those are the very hips that you should never touch with a knife. They were quite good hips to start with and would have been better with rest. They should be left alone, because if the patient is made to rest operation is unnecessary.

The group that needs surgery is very small. The more you see of your own cases in the later stages, the more you are inclined to narrow down, and I think the same thing is true of cortisone treatment. Perhaps that group will be benefited by cortisone.

But how long that benefit will last, I do not know. We know that the acrylic prostheses are going to pieces, and most people are now using metal.

I feel that surgery may be of benefit as a temporary measure but I should always try rest before I should agree to operate, or to give cortisone.

Intestinal Absorption of Iron in Anaemic Rheumatoid Arthritis Patients, before and during Administration of ACTH, Cortisone, or Compound F. By J. NORRIE SWANSON and WALTER BAUER, *Boston, Mass.*

A form of normocytic normochromic anaemia frequently accompanies rheumatoid arthritis. One characteristic is its unresponsiveness to orally administered iron, although it has been reported that intravenous iron has been used successfully to restore the blood picture to normal.

As part of an investigation into the nature of this anaemia, oral iron-loading studies were undertaken. The serum iron levels were measured before and at frequent intervals up to 4 hours after administration of 2 g. ferrous ammonium citrate by mouth to six normal subjects, six patients with rheumatoid arthritis and anaemia, and two with iron deficiency anaemia. The serum iron in the arthritic patients temporarily attained very much higher levels than in the control subjects, though not as high as in the iron-deficient patients. This suggested that the absorption of iron from the gut in these arthritis patients was actually better than normal, although the blood smears did not present a picture of iron deficiency anaemia. However, this interpretation may have to be qualified, as the rate of clearance of iron from the serum was not measured and may be slower in this form of anaemia. Even higher serum iron levels were found in three of the same patients when the experiment was repeated while they were receiving either ACTH, cortisone, or Compound F. It was also found in these and other patients suffering from various connective tissue diseases that within a few days of starting the hormones, the fasting serum iron level rose to about double its former value, but fell later.

Large doses of intravenous iron were given to one normal subject, two rheumatoid patients with iron deficiency anaemia, and five with the anaemia of rheumatoid arthritis. All of the patients had previously received adequate oral iron for at least one month without benefit. Within a few weeks after the intravenous administration of iron, the haemoglobin had risen by 3 to 4 g. in the iron-deficient patients, and by 1 to 3 g. in the rheumatoid anaemia patients. In only one of the latter was there any remission in the activity of the disease which could be associated with the reversion of the blood picture toward normality. For several hours after each injection, the amount of iron circulating in the serum was much greater than could have been bound to the metal-binding protein, and was presumably "free" in the form of iron polysaccharide. The significance of this temporarily unbound iron upon haemopoiesis was discussed.

Discussion.—DR. MORRIS ZIFF (*New York*): In the recent report of haemosiderosis after administration of iron, is that a contraindication, is that a definite problem?

DR. ERIC G. L. BYWATERS (*Taplow, Berks., England*): Dr. Swanson said that in cases where the haemoglobin stayed up or the iron stayed up, there was also a clinical remission. I should be glad to know which he thought came first, whether the remission came first and the iron stayed up, or *vice versa*.

DR. SWANSON: In answer to Dr. Ziff, I know no cases. Nissim, who first used this type of iron therapy, calculated that probably something in the neighbourhood of 30 g. would be required to produce a haemochromatosis. I personally know of patients who have had 3 g., and Dr. J. J. R. Duthie, who first interested me in this subject in Edinburgh, Scotland, and from whose series I quoted, has, I think, given 3 g. or maybe more. I do not believe the danger is a very real one.

In answer to Dr. Bywaters, I had hoped to be able to find out whether or not the arthritis remission preceded the recovery from anaemia, or was unrelated to it. Certainly the most spectacular blood response occurred in the man whose arthritis remission came on dramatically within 10 days of starting the iron therapy, but I am sorry that I cannot answer this question more definitely from the evidence of only a small series.

Juvenile Rheumatoid Arthritis: A Long-Term Follow-up. By ROBERT E. BARKIN, *Boston, Mass.*

In the last 35 years 45 cases of juvenile rheumatoid arthritis have been studied. Of this group, ten are now dead. One died in the fourth year of disease. (Average length of disease at death 13·5 years.)

The causes of death were: pneumonia, 3; pulmonary tuberculosis, 2; anaesthesia, 1; amyloid disease, 3; nephrosis, 1.

Twelve patients had severe systemic involvement ("Still's disease"). Of these, one is dead. Ultimate functional ability is poor in the group. Only one now has good function, six are bed-and-chair patients, one-third have moderate capacity as opposed to 70 per cent.

of the milder cases. Only two of the twenty cases with disease over ten years have complete functional ability.

Many feel that activity is limited to a few years, and by puberty, but our data indicates otherwise. Of twenty living patients with disease over 10 years, sixteen have continuous or recurrent activity. Recurrences and prolonged activity are the rule.

In our group, juvenile rheumatoid arthritis is a serious disease of prolonged or recurrent activity, considerable mortality, low incidence of complete recovery, and usually functional impairment.

Discussion.—DR. DAVID H. KLING (*Los Angeles, Calif.*): What therapy did these patients receive?

DR. DOUGLAS TAYLOR (*Toronto, Ont., Canada*): Little was said regarding the local care of the joints to prevent deformities, although presumably such measures were carried out. I believe this to be most important because attention these days seems to be focused largely on the treatment of arthritis by drugs.

The term "combined treatment" now seems to mean a combination of drugs. I suggest that the term "*total treatment*" be used, to emphasize the need for treatment of individual joints along with systemic measures.

Everyone stresses the need for "rest" in arthritic patients, but it should be emphasized that simply resting in bed does not necessarily rest a joint or the spine. This can be accomplished only by immobilization, using intermittent splinting or traction, with other local treatment, such as heat, massage, and graded exercises.

DR. BERNARD M. NORCROSS (*Buffalo, N.Y.*): The entire subject of juvenile rheumatoid arthritis is confused but I think we shall gradually gain a better understanding of these patients. His group is a selected one and probably more severe than the average group seen in private practice which may account for the more serious prognosis. Four years ago, we reported a group of 28 patients, having had excellent results in over 60 per cent. of them, and since that time, we have had no reason to change our opinion.

In our experience, only about 10 per cent. of our patients have had so-called Still's disease (those with systemic involvement). There is no question that this group has a poorer prognosis. I agree with Dr. Barkin that many patients have prolonged or multiple periods of activity. I am convinced that the prognosis will be improved with the use of hormone therapy.

DR. HANS WAINE (*Boston, Mass.*): Material of this kind is very hard to obtain. I should like to ask whether Dr. Barkin's studies included any inquiry into the familial incidence of rheumatic disease, and also whether Dr. Barkin can suggest any way of dealing with the growth disturbances in Still's disease.

DR. JOSEPH J. BUNIM (*Brooklyn, N.Y.*): Dr. Barkin has filled a longstanding gap in our knowledge of the natural course of juvenile rheumatoid arthritis. We have good reports on the natural history of rheumatoid arthritis in adults but, to my knowledge, no complete report of a substantial number of cases of juvenile rheumatoid arthritis has yet appeared.

He makes a distinction between severe systemic disease and cases that did not start with such manifestations. Like many others, he uses the term "Still's disease" for the first group, but I hope we shall find a more satisfactory term.

I think the American Rheumatism Association has for many years tried to delete the term "Still's disease" from our nomenclature and to substitute "juvenile rheumatoid arthritis", and if the latter is to be divided into two sub-groups, Still's and non-Still's, I think it will add to the confusion.

It surprised me a great deal that in the group of patients whose onset was characterized by the severe systemic involvement, with hepatomegaly, splenomegaly, serositis, and high fever, the mortality rate was relatively low. Only one of the eleven patients who died (in an average period of 13 years from onset to death) belonged to this group which started with very severe systemic manifestations. In other words, the mode of onset is no prognostic index as to length of life, though it is a guide to progress as to function of the joints.

DR. RALPH M. PATTERSON (*Hot Springs, Ark.*): I should like to ask Dr. Barkin what he thinks of splenectomy in the management of Still's disease.

DR. HARRY A. FELDMAN (*Syracuse, N.Y.*): Referring to the last speaker, we have followed for 18 months, a child who is seriously ill with Still's disease which came on 2 or 3 years after he had had the spleen removed for traumatic reasons.

DR. BARKIN: In answer to Dr. Kling and Dr. Taylor, the therapy has been conservative, with an attempt at prevention of deformities with shells, exercise, heat, and orthopaedic measures, and none of these children has had gold or cortisone. Obviously, over these many years the hospital has not been able to follow all the patients continuously, and some have visited around, as arthritics tend to do. So I feel sure that they have not had continuous good treatment, which would require hospital treatment or a close follow-up for many years.

I do not know how to explain the discrepancy between Dr. Norcross's figures and ours. He mentions 60 per cent. recovery. I wonder if that means complete recovery? One must follow these patients for many years before one can be reasonably sure they have recovered. Several of our patients had recurrences after many years of inactivity.

In answer to Dr. Waine, I believe that about 20 per cent. have a family history of rheumatic disease.

I know of no good way of dealing with growth disturbances, except to prohibit the excessive use of weight-bearing joints during periods of activity. We are not sure of the long-range effects of the steroids on the epiphyses in this disease.

As in the adult disease, the children die not of arthritis, but of a variety of other things.

I have had no experience with splenectomy in juvenile arthritis.

I do not know why only one of the children with the severe systemic or Still's form of the illness has died, as compared with ten of the others.

Management of Haemophilic Arthritis. By HENRY H. JORDAN, *New York*.

During the past 2 years, considerable progress may be recorded in the diagnosis and treatment of haemophilic arthritis. Almost every haemophiliac who survives infancy sooner or later shows joint involvement,

frequently complicated by severe flexion contractures, particularly at the lower extremities. Of 25 patients between the ages of 2 and 45 years severely crippled by haemophilic arthritis, most gave a history of inability to stand or walk for many years. Destruction of several articulations of the upper and lower extremities occurred more often than involvement of only one knee joint. Bony ankylosis is rare; it was seen in two patients, one suffering from destruction by haemophilic arthritis of every joint of the upper and lower extremities.

A large series of *x*-ray films permitted further clarification of the diagnostic characteristics. Restoration of articular function was possible to a greater extent and in a shorter period of time than originally anticipated in view of the *x*-ray films. The first objective of treatment is correction and stabilization of the lower extremities.

Proper evaluation of the patient's personality and physical condition, the apparently cyclic pattern of spontaneous bleeding, and his response to drugs and transfusions, are of great importance for the success of rehabilitation as well as for the prevention of crippling joint involvement.

The preparation and handy storage of quick-frozen group specific or pooled plasma permits greater activity in the correction of the deformities without undue risk. The marked vulnerability of the cystic juxta-articular bone in haemophilic arthritis deserves special attention. Strict adherence to the principle of " subliminal forces " for the correction of deformities and the development of apparatus to maintain correction and permit ambulation produced most satisfactory results in the group presented. With increasing experience treatment has to some extent been standardized.

Panel Discussion on " Treatment of Acute Rheumatic Fever with ACTH, Cortisone, and Acetylsalicylic Acid (Preliminary Report) ". Participants: DAVID D. RUTSTEIN (*Boston, Mass., moderator*); MARJORIE T. BELLOWS (*New York*), ERIC G. L. BYWATERS (*Taplow, England*), ALBERT DORFMAN (*Chicago, Ill.*), EDWARD E. FISCHEL (*New York*), JAMES E. FLETT, JR. (*Denver, Col.*), A. BRADFORD HILL (*London, England*), JOHN D. KEITH (*Toronto, Canada*), CURRIER MCEWEN (*New York*), BENEDICT F. MASSELL (*Boston, Mass.*), and CHARLES H. RAMMELKAMP (*Cheyenne, Wyo.*).

A co-operative study was organized by the Committee on Criteria and Standards of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association, and the Medical Research Council of England, for the collection and co-ordination of uniform data in a group of thirteen participating research centres in the United Kingdom, the United States and Canada.

The principal investigators of the co-operating research centres have planned and agreed upon a uniform experimental design of this therapeutic trial. The statement of protocol of this study defines diagnostic criteria, allocation of cases, therapeutic regimen, and clinical laboratory, and recording procedures. Results are currently transmitted on uniform record forms for correlation at the co-ordinating centre. Patients with rheumatic fever have been randomly selected for treatment with ACTH, cortisone, or acetylsalicylic acid during acute episodes of rheumatic activity.

In this panel discussion, a preliminary report was made of the results to date of the comparative effects of these agents on certain features of the acute course of the disease. The discussion itself was off the record.

BOOK REVIEWS

Kurzwellentherapie. By E. Schliephake. 5th ed. 1952. Pp. 256. Piscator-Verlag, Stuttgart. (36 DM; 63*s.*)

The author, who is Professor of Medicine at Wurzberg, has had over 25 years' laboratory and clinical experience in this speciality. This book not only sets out his own theoretical views and personal contributions in this field, but also embodies the experimental and clinical results of other workers.

After a short historical introduction, the author divides his book into two parts: Section A—physical and physiological (101 pages), and Section B—technical and clinical (137 pages, excluding the reference list and index).

Section A begins with considerations of elementary physics, definitions of units, and an explanation of such conceptions as "wave-length" and "frequency". A wave-length of less than 10 m. is referred to as ultra-short wave and one within the range 10-100 m. as short wave. For therapeutic purposes wave-lengths from 0·1 to 30 m. are used. In the author's view, the correct choice of wave-length is just as important as the size of the dosage and the choice and positioning of the electrodes.

The theoretical aspects of the action of short waves on biological systems are illustrated from experiments on bacterial cultures, isolated tissues, and small laboratory animals. The author considers that short waves act at molecular level, both on electrolytes and colloids, and quotes experiments carried out on purely chemical systems. He shows that their application to specific organs can produce marked changes in the blood chemistry as well as in the red and white cell counts, sedimentation rate, and viscosity. The increase in temperature at the site of application observed on treatment may therefore be due to factors other than local vasodilation. Experiments quoted also show the essential difference between short-wave therapy and diathermy. Whereas the effects of the latter appear to be concentrated at the periphery, short waves, by reason of their greater penetrating power, exert their maximum effect on deep structures. Furthermore, in short-wave therapy the electrode plates are held at a distance from the body, whereas in diathermy they are in direct contact.

In Section B, the first three chapters describe the types of apparatus in common use, their management, and the methods for measuring dosage. The choice of electrodes, their orientation and "distancing" from the body, and the choice of wave-length and size of dosage are discussed in relation to the site and nature of the complaint. One of the main dangers is localized overheating, which can result in serious burns, and a number of precautionary measures and contrivances designed to guard against this are shown. The relative merits of condensers and coils for producing the electro-magnetic field are discussed.

The fourth chapter deals with the application of short-wave irradiation to the production of artificial pyrexia, and the fifth with the rationale of short-wave therapy in individual diseases. The text is illustrated by case reports, including temperature charts, and *x*-ray plates taken before and after treatment. A glossary at the end of the book summarizes this chapter in tabular form, the last columns giving briefly the results likely to be expected. Where, in the author's experience, these have been disappointing he says so. This summary is only meant to indicate in general terms the routine likely to give satisfactory results in any particular condition. In the final summing up, it is emphasized that at present no hard and fast rules can be laid down but that most cases must be considered individually, the practical experience of the physician being often the most important factor in success. A final chapter, appearing for the first time in this edition, deals with the recent application of short-wave irradiation to diagnosis, a matter which appears to be still under investigation.

The second section is enhanced by some excellent illustrations, but in the first section some of the graphs and circuit diagrams are inconveniently small and the accompanying script almost microscopic. Two other similar complaints might be made. Firstly, the alphabetical reference list at the end is arranged in *solid blocks*. Inconveniently small print and the usual abbreviations assist to make them difficult to decipher. The more usual practice of tabulating references is much to be preferred. A second difficulty is the not infrequent use of abbreviations in the text, such as UKWD (for ultra-short wave irradiation), BSG (for blood sedimentation rate), and HED (about which the reviewer is still mystified). In future editions, a short glossary of these abbreviations would be an advantage to non-German readers.

From the rheumatologist's point of view this book may prove disappointing, only about 6 pages being devoted specifically to the rheumatic diseases. A footnote states that a monograph on rheumatism by the author is now in the press so that more detailed information should soon be forthcoming. In general, the results obtained are good, provided long-term treatment is undertaken, although in some cases the beneficial results do not become apparent until some weeks afterwards. Combination with salicylates or gold therapy is often advantageous.

But the book should certainly enable the postgraduate student wishing to specialize in physical medicine to form a good general picture of short-wave therapy, provided he is armed with the requisite technical dictionaries and a certain amount of perseverance. Into a relatively small book the author has succeeded in packing an immense amount of factual material, much of which it would probably be difficult to find elsewhere.

H. T. FAWNS.

Canadian Arthritis and Rheumatism Society, Handbooks for Patients, 1952.

(1) What you should know about Arthritis. Pp. 12. (10 *cts.*)

(2) Rheumatoid Arthritis. Pp. 24, 11 illus. (20 *cts.*)

In the first pamphlet the general problem of arthritis and rheumatism is discussed sensibly and in sufficient detail to cover many of the points which will be raised by the patients and their relatives. It is pointed out that rheumatoid arthritis is a disease of the whole body and not only of the joints, and that treatment consists of a carefully balanced programme of rest combined with exercise and may include more specialized types of treatment such as gold salts, cortisone, and orthopaedic measures. There are excellent short descriptions of ankylosing spondylitis, osteo-arthritis, fibrositis, and rheumatic fever, which are encouraging rather than depressing, but face the facts with reality.

A general chapter points out certain features of the rheumatic group of diseases which are important for the patient to know: That correct diagnosis is the key to successful treatment; that generalizations with regard to the rheumatic group of diseases are dangerous; that different treatment is necessary for each type of rheumatic disease; that there is no evidence that any special form of food or diet cures any of this group of diseases; that many kinds of rheumatism never disable; and that although cortisone and ACTH have not proved so easy to use or so successful as was hoped at first, they have opened up new avenues for research.

The second pamphlet deals with rheumatoid arthritis alone and in more detail, giving advice and encouragement as well as practical points in treatment and explaining the reason for some of the measures undertaken. There is an excellent chapter on the need for adequate rest, the best positions of the body during rest to prevent deformity, and simple methods of applying heat, and a section on therapeutic exercises from which the physician can pick the ones required. More specific measures such as gold and hormone treatment are described, with reasons why they form only part of the whole regime and an explanation of some of the dangers which may necessitate their being stopped.

There is also a small illustrated section on self-help devices, including valuable gadgets for putting on socks and shoes, simple eating utensils for deformed hands, and other measures to help the arthritic overcome his disabilities.

These pamphlets were designed by the Canadian Arthritis and Rheumatism Society particularly for patients with rheumatic disease in Canada, but they could be used with benefit throughout the English-speaking world. In a few pages they give sensible and encouraging advice and are a model of the type of written instruction, which may be handed out by the doctor to the patient.

OSWALD SAVAGE.

Arthritis and Rheumatism—The Patient's Guide to Treatment. By David E. Rodger and G. M. Miller. 1952. Pp. 72, 52 illus. Burns and MacEachern, Toronto.

This small book has received the approval of the Canadian Arthritis and Rheumatism Society whose objects and organization are listed as its third part. As the foreword states, its aim is to help the patient understand his disease and to give simple advice on treatment, particularly to those who may be isolated from medical help for long periods in a Canadian winter. The first two parts are by the doctor and the physiotherapist and it is difficult to say which is the better. The doctor gives sensible short descriptions of the commoner rheumatic diseases, and his comments on the drugs used in treatment are in line with modern concepts except for his pessimism about the value of gold salts. Diet, climate, physiotherapy, and the approach of the patient to his disease are treated with sagacity. In the physiotherapist's story her aspect of the various conditions is well stated though non-articular rheumatism is dismissed in only a few lines. Practical advice on such subjects as clothing, footwear, crutches, posture, and simple methods of applying heat are excellent. A series of exercises is well described, many with illustrations, but their application might have been clarified if the rheumatic conditions in which they are particularly appropriate had been named.

The authors are to be congratulated on producing a book full of wisdom and with good encouraging advice which may be read with advantage by many patients suffering from rheumatic disease and also by doctors and physiotherapists.

OSWALD SAVAGE.

The Merck Index. Sixth edition, 1952. Pp. 1167. Merck and Co., Inc., Rahway, N.J., U.S.A. ($7.50, thumb index edition $8.)

This work needs no introduction to those engaged in research problems with a chemical background. From its first appearance in 1889 its usefulness was assured, and each successive edition has grown in size in proportion with the ever-widening fields of chemistry. That it should reach its sixth edition is proof of its popularity and the soundness of its contents, and the demand for the present edition has already been so great as to necessitate a second printing of 25,000 copies.

The work has been completely revised and now contains more than 8,000 descriptions of individual substances, more than 2,000 structural formulae, and about 20,000 names of chemicals and drugs alphabetically arranged and cross-indexed. New features include a table of standard buffers for the calibration of *p*H measurements; a table of radioactive isotopes giving their half lives and type of radiation; and a table of names in current medical use for radioactive elements and components.

Each main entry indicates the preferred chemical name, other chemical names, common or popular names, generic and trade names. Trade-mark listing is as complete as possible and thoroughly cross-indexed.

A new section contains more than 300 organic "Name" reactions with original and review references, together with a description and structural representation of each reaction. There is an up-to-date periodic table, a table of international atomic weights, and close on 150 pages of appendices on such subjects as coal-tar colours, thermometric equivalents, anti-freeze mixtures,

refractive indices of liquids, saturated solutions, percentage solution tables for apothecaries, first-aid in poisoning, and atomic weights and their multiples and logs.

Properties and sources of substances, preceded by methods of preparation, with literature references, are given, followed by an indication of their uses, whether industrial, medical, or veterinary. Industrial hazards toxicities, and other safety factors are also mentioned.

The work was prepared by the Technical Information Department of Merck's Research and Development Division; in addition to members of Merck's Scientific Staff, many outside consultants have collaborated in the compilation and checking of information. It is printed in clear type on English-finish paper by Quin and Boden of Rahway, N.J., and bound in an attractive dark blue, gold-lettered, Fabrikoid cover which is resistant to water, acid, and mildew. The thumb-index is a great time-saver in the search for references.

It is difficult to imagine any scientific library without a copy of this encyclopaedia of chemicals and drugs, which cannot fail to prove invaluable to chemist, pharmacist, physician, dentist, and veterinary surgeon.

G. N. MYERS.

BRITISH MEDICAL ASSOCIATION

SCHOLARSHIPS IN AID OF SCIENTIFIC RESEARCH

The Council of the British Medical Association is prepared to receive applications for Research Scholarships, as follows:

ERNEST HART MEMORIAL SCHOLARSHIP, of the value of £250.

WALTER DIXON SCHOLARSHIP, of the value of £250.

ONE OR MORE RESEARCH SCHOLARSHIPS, each of the value of £200.

These Scholarships are given to candidates whom the Science Committee of the Association recommends as qualified to undertake research in any subject (including State Medicine) relating to the causation, prevention, or treatment of disease.

Applications are also invited for the following:

INSOLE SCHOLARSHIP, of the value of £250, for research into the causes and cure of venereal diseases.

Each Scholarship is tenable for one year, commencing on October 1, 1953. A Scholar may be re-appointed for not more than two additional terms. A Scholar is not necessarily required to devote the whole of his or her time to the work of research, but may be a member of H.M. Forces or may hold a junior appointment at a university, medical school, or hospital, providing the duties of such appointment will not, in the opinion of the Science Committee, interfere with his or her work as a Scholar.

Applications for Scholarships must be made not later than March 31, 1953, on the prescribed form, a copy of which may be obtained from the Secretary.

Applications are required to furnish the names of three referees who are competent to speak as to their capacity for the research contemplated.

A. MACRAE, *Secretary.*

BRITISH MEDICAL ASSOCIATION HOUSE,
Tavistock Square, London, W.C.1.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

REPORTS FROM MEMBER COUNTRIES

BELGIUM

A research foundation has been created by the four Belgian universities in order to study the problems of the rheumatic diseases, and a chair of rheumatology has been established which is now held by Professor Michotte.

Recently the celebrations of the 25th anniversary of the Belgian League were attended by many leading rheumatologists from other countries.

CZECHOSLOVAKIA

Regular scientific meetings are held and the Czech League offers substantial monetary awards for publications on the rheumatic diseases. Five principal consulting physicians have been appointed to rheumatism centres. The League supplies lecturers in rheumatology for post-graduate courses, and in 1951 these were attended by over 200 physicians.

DENMARK

Four laboratories have been established for research work connected with the rheumatic diseases, under the supervision of the University of Copenhagen. In one, pathological studies are being carried out on *post-mortem* material collected from all over the country; another is concentrating on the physiological characteristics of the synovial membrane and on problems connected with salicylic acid; a third is working on the histo-chemistry of the mesenchymal tissues and of hyaluronic acid in particular; and lastly the State Serum Institute laboratories for endocrinological research, immunology, serology, and bacteriology, undertake work on particular problems of the rheumatic diseases.

In addition there are three large clinical research departments which have recently been concentrating on work with cortisone and ACTH, particularly the latter. It is intended to establish permanent departments for rheumatology and physical medicine at Denmark's two universities, Copenhagen and Åarhus.

FINLAND

Work in the field of rheumatic diseases is progressing rapidly and a new hospital for 300 rheumatic patients has been opened in Heinola with the prospect of another in Helsinki in the future. Regular scientific meetings are held and their proceedings published.

FRANCE

The national league, founded 20 years ago by Dr. Henri Forestier, divides its activities under three headings, scientific, social, and international.

Scientific meetings are held on the second Wednesday in each month at the Hôpital Cochin in Paris and many of the discussions are subsequently published. Meetings have also been held at other centres on such subjects as " Diseases of the Vertebral Column " in conjunction with the French orthopaedic society, " The Relation of Rheumatism to the Endocrine Glands ", " Rheumatism of the Sacro-iliac Joints ", and " Chronic Juvenile Rheumatism ".

The social side of the plan aims at the formation of medical teams to deal with the problems of these diseases. That these efforts are being successful is shown by their achievement in sponsoring the creation of a chair of clinical rheumatology at the Hôpital Cochin; this is now held by Prof. Coste with Prof. de Sèze as his associate. The teaching of rheumatology has been organized by this faculty and steps have been taken to create an official status for specialists in rheumatology as has been done in Great Britain. A permanent commission on rheumatism has been established at the Ministry of Health and as a result there has been an increase in the number of diagnostic centres both in Paris and the provinces, and public money has been allocated for this purpose and for the purchase and distribution of cortisone and ACTH.

In the international sphere the French branch maintains a close liaison with neighbouring countries and other members of the European League.

ITALY

There has been a revival of interest in the rheumatic diseases since the war. In 1948 the " Italian Society for the study of Rheumatism and combating Rheumatic Disease " was formed officially at a meeting at Acqui during which papers were presented on certain clinical syndromes and on the pathological anatomy of osteo-arthritis. Since then

annual meetings have been held and the proceedings published.

Specialized centres now function in the University Clinics of Genoa, Rome, Catania, Bologna, Bari, Milan, Cagliari, Padua, and Turin, with out-patient departments and wards and access to the laboratories and other facilities of the parent hospitals.

At the meeting of the European League in Barcelona in 1951 the Italian rheumatological society was represented by Professor Sabatini.

PORTUGAL

In the last few years a rheumatic association has been founded and a special clinic opened in the University Hospital, Lisbon. It is proposed to form three centres under state control in the north, south, and central districts. The Lisbon centre is already established with clinical, social, and research departments.

SPAIN

In 1950 a special course of lectures on rheumatology was held in Madrid with a number of guest lecturers including Dr. W. S. C. Copeman, President of the European League. A tremendous amount of organization and preliminary work was carried out by Spanish rheumatologists for the 1951 Barcelona Congress which attracted a large international gathering. The success of these meetings was a tribute to their efforts.

SWEDEN

There is a scientific society limited to medical members supported by a rheumatological research council founded by the late King and a national social organization with some 10,000 members. Owing to the decline in the number of tuberculous patients more beds have been made available for rheumatic cases. It is considered in Sweden that the early treatment of cases of the rheumatic diseases should be carried out in specialized units and that later such cases may be transferred to general hospitals. It has been estimated that 3,000 beds are required for this purpose.

SWITZERLAND

The organization is based on a cantonal system and free consultations are held for sufferers in Geneva, Basle, and Zürich. It is proposed to build a Thermal hospital at Loeche-les-Bains combining medical, spa, physiotherapy, and orthopaedic treatments. In Zurich a clinic with 60 beds is to be opened for rheumatic cases.

LIGUE INTERNATIONALE CONTRE LE RHUMATISME

EIGHTH INTERNATIONAL CONGRESS, 1953

The eighth international congress of the Ligue Internationale contre le Rhumatisme will be held from August 24 to 28, 1953, at Geneva, Switzerland, and Aix-les-Bains, France. A special meeting in connection with the congress will be held at Zürich, Switzerland, on August 29. The programme of scientific discussions will be arranged as follows:

1. Tissus conjunctifs et rhumatisme.
2. Stéroïdes dans le traitement du rhumatisme.
3. Résultats éloignés de la chirurgie du rhumatisme de la hanche.
4. Réadaptation professionnelle.

Workers from several centres in Europe and America have already promised reports on their researches. Papers, which should be of 10 minutes' duration, should be sent to the secretary of the National League to which the applicant belongs not later than February 1, 1953.

Further information may be had from Prof. K.-M. Walthard, Institut de Physiatrie, Hôpital Cantonal, Genève, Suisse. Applications for registration should be addressed to the nearest agency of the American Express Company who are organizing the travel arrangements.

HEBERDEN SOCIETY

Clinical Meeting.—A meeting was held at the Postgraduate Medical School, Hammersmith, London, on October 24, 1952. Professor McMichael took the Chair. He welcomed the members of the Society and in particular a number of distinguished French physicians who had come as guests. The following cases were shown:

(1) Dr. R. I. S. Bayliss: A man, aged 28, with pulmonary tuberculosis which had been treated by streptomycin, P.A.S., and a right thoracoplasty, with steady improvement, had 3 months previously developed an acute arthritis involving the left ankle and knee with sore throat and fever. This condition had at first been regarded as rheumatic fever but had later presented the typical clinical picture of rheumatoid arthritis.

Dr. Forestier stated that in his opinion there was no connection between rheumatoid arthritis and tuberculosis.

Professor de Sèze commented that such an acute onset of rheumatoid arthritis was more frequent in males than in females.

(2) Dr. I. Meanock: A man, aged 28, with Reiter's syndrome had urethral discharge, pain in the left chest, fever, and keratodermia blennorrhagica, but no evidence of gonococcal infection. *X* rays of the feet showed early erosions of the metatarsal heads. A course of aureomycin was followed by improvement.

Dr. Perlès discussed the importance of the absence of conjunctivitis and dysentery and said that in France the existence of "Reiter's syndrome" was doubted.

Dr. Hubble said that he had found this condition common in Derby, and had obtained good results with hyperthermia produced by intravenous T.A.B.

(3) Dr. E. G. L. Bywaters: A woman, aged 39, had disseminated lupus erythematosus which started with classical rheumatoid arthritis after a miscarriage. She had later developed pink cutaneous nodules with small areas of central necrosis on both hands, together with "nail-edge" lesions, and recently L. E. cells had been found in the blood on two occasions. Slides were shown of a similar case in which gangrene had developed in one hand.

Professor Coste said he had seen similar cases but had never found L.E. cells in the blood.

(4) Dr. G. R. Fearnley: A woman, aged 30, had ankylosing spondylitis which started at the age of 18 and had responded to deep *x*-ray therapy. Her sister also had a similar condition but in her case there had been involvement of the peripheral joints and at a later stage she had developed kyphosis with evidence of erosion of the third lumbar vertebra which was considered to be an osteoporotic collapse.

Dr. Forestier stressed the frequency of tuberculous changes in the spines of cases of ankylosing spondylitis though there was no evidence of this in the case shown.

Dr. Françon also contributed to the discussion.

(5) Dr. C. Fletcher showed *x*-ray films from cases of "Caplan's syndrome", a radiological condition which has been found in coal miners under observation for pneumoconiosis. It consists of circumscribed shadows throughout both lung fields which have developed from the diffuse massive fibrosis seen in this condition and have been present in some cases before the onset of rheumatoid arthritis. From the radiological appearance, the lesion is considered to be tuberculous but this has not yet been proved.

The French visitors were later entertained to Dinner by Lord Horder and the Executive Committee of the Society.

Heberden Oration.*—The next day, October 25, Lord Horder delivered the Heberden Oration and was presented with the Heberden Medal by Sir Henry Cohen, President of the Society.

* The Oration will be published in a later issue of this Journal.

NEW YORK RHEUMATISM ASSOCIATION

The Fall Meeting was held at the New York Academy of Medicine on November 12, 1952. The President, Dr. Charles Ragan, took the chair. A paper on "Lupus Erythematosus Disseminatus" was read by Dr. J. R. Haserick (*Cleveland*), and the discussion was opened by Dr. L. J. Soffer (*New York*).

The Spring Meeting will be held on April 8, 1953, at Cornell University Medical College. Members desiring to present papers at this meeting should submit titles and brief abstracts to Dr. Bernard Rogoff, 33 East 61 Street, New York City, before February 15, 1953.

CANADIAN RHEUMATISM ASSOCIATION

The Annual Business and Scientific Meeting was held on June 9 and 10, 1952 at the Banff Springs Hotel, Banff, Alberta, and the following papers were presented.

Dr. A. W. BAGNALL (*Vancouver*). **Intermittent Use of Cortisone in the Long-Term Management of Rheumatoid Arthritis.**

Dr. C. E. G. ROBINSON (*Vancouver*). **Problems of a Provincial Director of the Canadian Arthritis and Rheumatism Society.**

Dr. MAURICE YOUNG (*Vancouver*). **Cortisone in Rheumatic Fever.**

Dr. F. W. B. HURLBURT (*Vancouver*). **Continuous Oral Cortisone in Rheumatoid Arthritis.**

Dr. H. V. CRANFIELD (*Medical Director, The Mutual Benefit Health and Accident Association*). **Conservative Treatment of the Herniated Intervertebral Disk** (moving picture).

Drs D. C. GRAHAM and J. NORRIE SWANSON (*Toronto*). **Current Therapy of Gout.**

Drs HAROLD ROBINSON and C. J. COLBECK (*Vancouver*). **Peri-Arthritis and Coronary Disease.**

Drs D. E. RODGER and T. E. HUNT (*Regina*). **Juvenile Rheumatoid Arthritis, Long-Term Therapy with Cortisone.**

Drs T. E. HUNT and R. C. ANDERSON (*Regina*). **Cortisone and Hydrocortisone (Compound F) combined with Orthopaedic Measures in the Correction of Rheumatoid Deformities.**

Drs WALLACE GRAHAM and J. B. ROBERTS (*Toronto*). **Intravenous Colchicine in Gouty Arthritis.***

Dr. L. G. JOHNSON (*Montreal*). **Continuous Cortisone in Rheumatoid Arthritis.**

Drs ELDON BOYD, H. G. KELLY, and J. G. HILL (*Kingston*). **Blood Lipid Fractions in Rheumatoid Arthritis, Effects of Cortisone.**

* To be published in the March, 1953, issue of this Journal.

URUGUAYAN RHEUMATOLOGICAL SOCIETY

A congress of rheumatologists will be held in Montevideo from March 8-12, 1953. At this time of year the climate is most pleasant for travelling and sightseeing, and it is proposed to diversify the scientific meetings with visits to places of interest, including the spa (*zona balnearia*) at Punta del Este.

Members of the various national branches of the Ligue Internationale contre le Rhumatisme, and other workers in this field, are invited to attend. Further information may be had from the Secretary-General, Dr. Benito Barrós, Av. Agraciada No. 1464, Piso 13, Montevideo, Uruguay.

Papers will be given on various aspects of rheumatology, with special emphasis on Rheumatoid Arthritis, Rheumatic Fever, and the Social Problems of Rheumatism. A programme containing abstracts of the papers accepted will be published in January, and those wishing to contribute to the discussions thereon are asked to notify the Secretary as soon as possible. The complete proceedings including the discussions will be published after the congress.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism: Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous): Sciatica: Gout: Non-Articular Rheumatism: General Pathology: ACTH, Cortisone, and other Steroids: Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section " ACTH, Cortisone, and other Steroids ", includes abstracts and titles of articles dealing with steroid research, which although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Effect of ACTH and Cortisone on Rheumatic Carditis. Observations on Eighteen Cases. KUTTNER, A. G., BALDWIN, J. S., MCEWEN, C., BUNIM, J. J., ZIFF, M., and FORD, D. K. (1952). *J. Amer. med. Ass.*, **148**, 625. 1 fig., 10 refs.

Of eighteen patients observed in an investigation in New York, twelve were suffering from a first attack of rheumatic fever and six from a recurrent attack; all were known to have rheumatic carditis. Corticotrophin or cortisone was given to four of the twelve patients in their first attack within 7 weeks of the onset of symptoms and to the others several months after onset. In all cases the hormones caused a marked diminution in toxic symptoms and improvement in the general condition. Pericarditis and congestive heart failure seemed to respond most favourably to treatment. In two patients the authors concluded that the administration of hormone had had a life-saving effect.

On the whole, it was difficult to assess the exact effect of the hormone on the carditis. In some cases the activity of the carditis gradually subsided after cessation of hormone therapy; in others there was an immediate relapse. In all twelve patients who were suffering from a first attack, however, rheumatic carditis was present six months after treatment ceased. Similar results were found in patients suffering from recurrent attacks.

The authors suggest that it is possible that corticotrophin and cortisone, by suppressing the activity of the disease, may reduce cardiac fibrosis and scarring, but this was not proved. They conclude that their results do not show that the hormones significantly decreased the duration or severity of cardiac damage, and that further study of larger numbers is needed. *W. Tegner.*

Rheumatic Fever during the First Few Years of Life and its Differentiation from Endocardial Fibrosis. LOGUE, R. B., and HURST, J. W. (1952). *Amer. J. Med. Sci.*, **223**, 648. 13 refs.

The authors suggest, as the result of recent experience, that the frequency of occurrence of rheumatic fever at or below the age of 5 years has been underestimated in the past. Amongst the possible explanations for this are the application of too rigid diagnostic criteria, the natural assumption that heart murmurs heard in the first few years of life are congenital in origin, and the frequent similarity of endocardial fibrosis. In a series of 26 children under 5 years of age treated and followed up by the authors, the diagnosis of rheumatic fever was established in four cases at necropsy, and in the remaining cases by the presence of characteristic features of rheumatic infection or the development of signs of rheumatic heart disease during a long-term follow-up. Points of value in differentiating rheumatic fever and rheumatic heart disease from endocardial fibrosis are listed.

W. S. C. Copeman.

Cortisone in Rheumatic Carditis. Some Preliminary Observations. CHAMBERLAIN, E. N., HAY, J. D., and FREEMAN, D. M. (1952). *Brit. med. J.*, **1**, 1145. 3 figs, 12 refs.

The authors present a preliminary report on a study, at hospitals in Liverpool, of the effect of cortisone on the manifestations of acute rheumatic carditis in twelve children and adolescents. Selection of the patients depended on the presence of signs of active carditis or pericarditis with friction or effusion, cardiac murmurs, or clinical evidence of cardiac enlargement together with other rheumatic signs and symptoms such as nodules, arthritis, fever, raised sleeping pulse rate, raised erythrocyte sedimentation rate (E.S.R.), and " rheumatic " rashes. Each case was seen by three observers. Most, but not all, of the patients were observed for one week or longer before treatment with cortisone acetate, which was given in doses of 50 to 100 mg. daily for 10 days to 5 weeks. The patients were followed up for several weeks or months after treatment had ceased.

Of three patients who died during treatment, one had responded with general improvement, reduction in E.S.R., and disappearance of arthritis, though the cardiac signs remained unchanged. The nine who survived showed an improvement in general health, and a fall in heart rate, temperature, and E.S.R., but no improvement in

cardiac signs or electrocardiographic pattern. In several cases there was evidence of water retention.

[This paper, while not presenting conclusive evidence for or against cortisone treatment in acute rheumatic fever, is a valuable contribution. Most clinicians engaged on similar studies would agree with the authors' tentative conclusions. The more important question of the effect of cortisone in the prevention of the long-term cardiac sequelae of rheumatic fever remains unanswered, and its investigation must clearly be undertaken on a much larger scale. Such an investigation is now in progress in Britain under the Medical Research Council in conjunction with a similar investigation in the United States.] See also report on p. 318. *G. Loewi.*

Coexistent Rheumatic Fever and Subacute Bacterial Endocarditis treated with ACTH and Antibiotics. NUMAINVILLE, L. J., and SCARPELLINO, C. J. (1952). *Amer. Heart J.*, **43**, 468. 2 figs, 4 refs.

A well-authenticated case of rheumatic fever with endocarditis due to *Staphylococcus aureus* in a man of 23 is described. Corticotrophin, penicillin, and, later, streptomycin and chloromycetin, to which the organism was sensitive, were given with good results. Corticotrophin was of definite benefit in the rheumatic process, and clinical evidence of septicaemia disappeared during its administration, although the organism could still be isolated from the blood. It is suggested that corticotrophin may be of value in the treatment of endocarditis in suppressing toxicity, but that it is hazardous without specific antibiotic therapy. *A. Paton.*

Acute Benign Pericarditis in Childhood: Comparisons with Rheumatic Pericarditis, and Therapeutic Effects of ACTH and Cortisone. FRIEDMAN, S., ASH, R., HARRIS, T. N., and LEE, H. F. (1952). *Pediatrics*, **9**, 551. 37 refs.

Since Barnes and Burchell, in 1942, first described the syndrome of acute benign pericarditis a number of cases in adults have been reported. So far as the authors are aware, the six cases here described are the first recorded in children.

The ages of the patients, three boys and three girls, ranged from 3 years to 12 years, and all were white children. The symptoms were limb pains (but without pain or swelling of the joints), fever, tachycardia, and general malaise. A pericardial friction rub was heard in all cases; the heart was enlarged and the pulse rate was 120 to 140 per minute. The changes in the electrocardiogram were those of classical pericarditis; no endocardial murmurs were heard. In two cases there were signs of congestive heart failure, and in four there was pleural or pulmonary involvement. The duration of the illness was 3 weeks to 3 months.

Aureomycin and chloramphenicol were without effect in treatment. In four cases, however, dramatic improvement, both in the general condition and in the cardiac signs, quickly followed a course of corticotrophin or cortisone; symptoms reappeared in three children, but yielded to a second course of the drug. During a follow-up period of 10 to 22 months, no cardiac enlargement was observed in any of the cases and the electrocardiogram was normal; in one case extrasystoles, which were first observed during the acute phase of the disease, were still present.

None of the classical signs seen in the heart and limbs in eight cases of acute rheumatic pericarditis (under observation at the same time) was found in these cases of benign pericarditis, and all the evidence indicated a different disease process in the two groups. Benign pericarditis is thought to be due either to a virus, possibly respiratory, or to an allergic reaction, but no evidence was found to support either theory. *Charles McNeil.*

Left Auricular Appendage in Mitral Stenosis. A Study of 15 Cases submitted to Valvulotomy. PINNIGER, J. L. (1951). *St. Thom. Hosp. Rep.*, **7**, 54. 8 figs, 20 refs.

This paper contains a brief review of the significance of the Aschoff node in the myocardium and its relation to clinical carditis and rheumatic "activity", followed by a detailed account of the histology of the left auricular appendage removed in fifteen cases of mitral stenosis subjected to valvulotomy at St. Thomas's Hospital, London. A tabular survey of the cases is given, correlating the available evidence of clinical "activity" in each patient with the appearance or absence of Aschoff nodes in the heart. In most cases one section was taken from each biopsy specimen, and in cases where more than one was taken there was not a great deal of difference between sections. Aschoff nodes were found in ten cases; and of the six of these in which the erythrocyte sedimentation rate (E.S.R.) is given, only two had an E.S.R. above 20 mm. in one hour. The endocardium was thickened in fourteen of the fifteen cases. Photomicrographs of the Aschoff nodes from three cases are reproduced. The myocardium showed some hypertrophy; in places there was mucoid degeneration and in others a patchy fibrosis. Pericardial changes were slight.

An attempt was made to confirm these findings by reference to nineteen cases of mitral stenosis in patients dying between 1944 and 1950 whose myocardium was available for *post-mortem* study: in six of these definite Aschoff nodes were present. The author considers that his findings give histological support to the view that activity of the disease process may persist in a latent form in many patients with clinically quiescent rheumatic valvular disease. *E. G. L. Bywaters.*

Cortisone and ACTH in the Treatment of Rheumatic Fever. JOHNSON, A. L., MCCALL, M. F., HARPUR, E. R., BURNS, A., and WOLMAN, B. (1952). *Canad. med. Ass. J.*, **66**, 225. 12 refs.

The authors, from McGill University, describe the results of cortisone therapy at the Children's Memorial Hospital, Montreal, in 39 children suffering from rheumatic fever; 26 of the patients received cortisone intramuscularly and seven orally, while six patients were given corticotrophin intramuscularly. In five patients with chorea, subsidence of the choreic manifestations was coincident with the administration of cortisone, but only in one case did the authors feel certain that the treatment had influenced the course of the illness.

Of the patients with rheumatic fever, five showed no apparent response to treatment; in the other cases the

effects of the hormone treatment on fever, pulse rate, joint pain, and erythrocyte sedimentation rate followed the usual pattern. Two patients had subcutaneous nodules, in one of whom a gradual reduction in size of the nodules occurred, with complete disappearance 7 weeks after starting the hormone therapy. Biopsy specimens of the nodules were obtained before cortisone administration and on the 20th day of treatment, but no difference was found in the histological appearances of these specimens. In seven children severely ill with acute carditis, corticotrophin or oral cortisone was employed because the shorter duration of action of these preparations would facilitate withdrawal of therapy should cardiac failure occur. A low-sodium diet was used in these seven cases and also in all but five of the other cases in the series. All seven cases of carditis showed an excellent response to hormone therapy within 48 hours; of the five patients who had no previous history of heart damage, three have remained without clinical evidence of cardiac disease.

Recurrence of symptoms occurred in five of the 39 cases 4 to 6 days after stopping treatment; in three of these there was evidence of carditis. Following an additional course of treatment they showed the usual elevation of erythrocyte sedimentation rate, but no clinical manifestations of recurrence. In four patients there were recurrent episodes of acute rheumatic fever 1, 2½, 4, and 6 months respectively after completion of hormone therapy. *C. E. Quin.*

Trial of Pyrocatechol-3-carboxylic Acid in the Treatment of Rheumatic Fever and Rheumatoid Arthritis and a Study of its Mode of Action. (Essai de l'acide pyrocatéchol-3-carboxylique dans le rhumatisme articulaire aigu et la polyarthrite chronique évolutive et étude de son action.) MICHOTTE, L. (1952). *Rev. Rhum.*, **19**, 230. 11 refs.

Pyrocatechol-3-carboxylic acid is one of the oxidation products of salicylic acid. On the assumption that it is formed in the human body after ingestion of salicylates, and that it may be the anti-rheumatic agent in sodium salicylate therapy, the author has carried out clinical and biological studies of this substance.

In a therapeutic trial in twenty cases of rheumatic fever, sodium pyrocatechol carboxylate was given in doses of 0·5 g. at 4-hourly intervals (3 g. in 24 hours). It appeared to be superior to sodium salicylate in that the same results were obtained with smaller doses, and the substance has very low toxicity. The erythrocyte sedimentation rate became normal in an average of 30 days: with large doses of sodium salicylate the average time is 4 weeks, and with cortisone 12 to 18 days. In the electrocardiogram the P-R interval was increased in eight cases, in six of which it returned to normal in an average of 26 days; it is unaffected by sodium salicylate therapy. Pyrexia abated in 48 hours, and arthralgia in an average of 12 days. The substance was found to have no effect on rheumatoid arthritis.

In experiments with rats, mice, and rabbits, the effects of sodium salicylate, cortisone, and sodium pyrocatechol carboxylate were compared. All three showed an antipyretic effect. Cortisone and sodium pyrocatechol carboxylate had a toxic, but reversible, effect on the cellular tissue of the spleen and testis, an effect not found with sodium salicylate. Ingestion of all three substances brought about a fall in the ascorbic acid content of the adrenal glands. *Kenneth Stone.*

Response of the Serum Polysaccharide Fractions and Protein Fractions following Cortisone Treatment of Patients with Rheumatic Fever. SHETLAR, M. R., SCHMIDT, H. L., LINCOLN, R. B., DEVORE, J. K., BULLOCK, J. A., and HELLBAUM, A. A. (1952). *J. Lab. clin. Med.*, **39**, 372. 4 figs, 16 refs.

A preliminary study was made of alterations of the serum polysaccharides and other serum factors occurring in five rheumatic fever patients under treatment with cortisone. The serum nonglucosamine polysaccharide, glucosamine polysaccharide, albumin polysaccharide, α-globulin polysaccharide, and serum heat coagulation values were all found to be greatly elevated prior to therapy, while the albumin percentage and albumin: globulin ratios were lowered. Following treatment with cortisone, subjective clinical improvement was promptly followed by decreases in the serum nonglucosamine and glucosamine polysaccharides, albumin polysaccharide, α-globulin polysaccharide and serum heat coagulation values, and by increase in albumin and in the albumin: globulin ratio. Recurrence of rheumatic fever, with a return of the serum factors to the original state, occurred in two cases after cessation of treatment.

It appears that the studies of the serum polysaccharide components, serum heat coagulation values, and albumin percentages may be valuable aids in the evaluation of rheumatic fever patients.—[*Authors' summary.*]

Fibrinoid Necrosis in Rheumatic Fever. GLYNN, L. E., and LOEWI, G. (1952). *J. Path. Bact.*, **64**, 329. 2 figs, 12 refs.

Fibrinoid material in subcutaneous nodules from cases of rheumatic fever has been examined histochemically. It differs from fibrin in its fibrillar structure as revealed by silver impregnation and by its resistance to tryptic digestion. It differs from collagen in its argyrophilia and in its intensely positive P.A.S. reaction. It resembles collagen in being attacked by trypsin after denaturation by heat or urea. Removal of polysaccharide by pectinase or extraction with potassium salts results in the simultaneous loss of the P.A.S. reaction and argyrophilia.

The fibrinoid change seems to be brought about by the infiltration of collagen with a polysaccharide-rich material, possibly a glycoprotein.—[*Authors' summary.*]

Changes in the Morphology and Permeability of the Capillaries in Acute Articular Rheumatism. (Alterazioni della morfologia e della permeabilitá dei capillari nel reumatismo articolare acuto.) PRATESI, G., and GAROFOLI, C. (1952). *Policlinico (prat.)*, **59**, 469. 2 figs.

The authors stress the importance of endogenous factors in the pathogenesis of rheumatic fever. At the University Medical Clinic, Rome, they investigated the changes in the morphology and the permeability of the capillaries in eighteen cases of active rheumatic fever and, for comparison, in eleven patients suffering from heart

conditions of rheumatic origin but in a phase of relative inactivity. The morphology was investigated by capillaroscopy, fragility by Göthlin's method, and the permeability of the capillaries by estimating the loss of liquid, the loss of proteins, and the protein content of the filtrate by Landis's technique. These examinations showed that patients suffering from active rheumatic fever show morphological changes in the capillaries, partly constitutional and partly acquired as a result of the increased permeability of their wall. There were no changes in capillary fragility. The authors attach great importance to the investigation of the small vessels in rheumatic disease. *J. Mester.*

Factors influencing Plasma Concentrations of Gentisate. MEADE, B. W., and SMITH, M. J. H. (1952). *Clin. Sci.*, **11**, 81. 4 figs, 15 refs.

In view of the recent introduction of sodium gentisate as a non-toxic substitute for sodium salicylate in the treatment of rheumatic fever, the factors influencing the gentisate concentration in plasma were investigated at King's College Hospital Medical School, London. In normal subjects peak plasma concentrations of gentisate occurred 2 hours after the administration of 3, 4, or 5 mg. by mouth 2 hours after a meal. The average plasma concentration of gentisate over a 5-day period was not significantly different whether 1 g. was given every 2 hours or 2 g. every 4 hours. No correlation was found between the dose of gentisate per kg. body weight and the plasma concentration attained, nor between the rate of excretion of the drug and the volume or *p*H of the urine, but in patients taking a fixed daily dose of gentisate its concentration in the plasma varied inversely with the fluid intake. When sodium bicarbonate was given at the same time, there was an increase in rate of absorption and a delay in that of excretion of gentisate, resulting in a higher concentration of gentisate in the plasma and its longer retention. This finding is particularly interesting in view of the more rapid excretion of salicylate when sodium bicarbonate is given.

Solutions of sodium gentisate should be freshly prepared at a *p*H of less than 8·5, the salt being unstable in alkaline solution; even neutral solutions exposed to daylight for 3 days lost 10 per cent. of their gentisate.

It is briefly reported that in three children with rheumatic fever given 12 g. of sodium gentisate daily, plasma concentrations of 6·5 to 15 mg. per 100 ml. were maintained with no reduction in alkali reserve during several weeks of treatment.

[It is clear from experience with patients and with animals that this substance is very much less toxic than sodium salicylate and is much better tolerated. Further reports on its therapeutic usefulness in rheumatic fever are awaited.] *Derek R. Wood.*

Q-T Interval during Active and Inactive Rheumatic Fever. FINKEL, S., and BALDWIN, J. S. (1952). *Pediatrics*, **9**, 410. 1 fig., 24 refs.

The authors studied the electrocardiogram (ECG) and clinical records of 208 children, aged 3 to 13 years, suffering from active rheumatic fever or chorea, and compared them with similar records of 79 normal children. The Q-Tc interval was prolonged in a significant number of children with rheumatic carditis and in a much smaller number of children with polyarthritis or chorea. In some of the children a prolonged Q-Tc interval was maintained during the inactive phase of the disease. The Q-Tc interval was found to exceed the upper limit of normal in 12·7 per cent. of normal children, and it was therefore considered that the single finding of a long Q-Tc interval should not be taken as indicating persistence of active carditis. *R. S. Illingworth.*

Sinus Bradycardia in Acute Rheumatic Fever. HIRSCH, J. G., and FLETT, D. M. (1952). *Ann. intern. Med.*, **36**, 146. 3 figs, 7 refs.

During the first 5 weeks of their stay in a U.S. Air Force hospital at Cheyenne, Wyoming, 59 of 106 young adult males with acute rheumatic fever showed electrocardiographic evidence of sinus bradycardia. Many of them had tachycardia during the febrile phase, followed immediately by a phase of sinus bradycardia lasting from 2 to 14 days. The heart rate then returned to a normal or elevated level. The bradycardia occurred in cases of all degrees of severity, but rather more commonly in those with a milder attack and those with a favourable prognosis. *R. S. Illingworth.*

A Follow-up Study of Tonsillectomy in Children with Rheumatism. (Katamnestische Beurteilung der Tonsillektomie beim kindlichen Rheumatismus.) NETZSCH, H. (1952). *Münch. med. Wschr.*, **94**, 971. 12 refs.

The author has attempted to assess the effects of tonsillectomy—so frequently suggested as a prophylactic measure on theoretical grounds—on the subsequent course of rheumatic fever (with and without endocarditis) and chorea minor by means of a 10-year follow-up study. Of the 319 patients studied, eighty had had their tonsils removed. On statistical analysis of the findings it was found that tonsillectomy appeared to reduce the incidence of recurrences of endocarditis and also to lessen the possibility of a fatal outcome, whereas it has no appreciable effect on the incidence of recurrence of joint symptoms. In chorea minor tonsillectomy would seem to be contraindicated, only two out of fifteen patients subjected to tonsillectomy failing to relapse, compared with 41 out of 81 whose tonsils were not removed. A study of larger numbers is desirable. *D. Preiskel.*

Pneumonitis in Rheumatic Fever. (Estudio anatomoclinico de la neumonitis reumatica.) CUELLAR, A., and PEREZ TAMAYO, R. (1951). *Arch. Inst. cardiol. Mex.*, **21**, 594. 16 figs, bibl.

The authors have investigated twelve consecutive cases of acute rheumatic fever seen at the Mexican National Institute of Cardiology. In eight cases the diagnosis of rheumatic pneumonitis had been made *in vivo* and in six of these was confirmed *post mortem*; in four cases the diagnosis was established only at necropsy. Sections of the lung were stained with hematoxylin and eosin, and Weigert's technique was used for elastic fibres and Río-Hortega's silver impregnation method for precollagenous fibres. Ten cases of chronic passive congestion were examined for control purposes.

The authors are of the opinion that pneumonitis is often present during the active stages of rheumatic fever, but that it is frequently masked by the signs and symptoms of cardiac insufficiency. The clinical manifestations are dyspnoea, cough, pain in the chest, cyanosis, and fever, with fleeting signs of consolidation in changing sites. The pathological changes are not specific, but are characteristic; there is increased capillary permeability, with necrosis of the walls of pulmonary alveoli and fibrinous exudate; some of the larger vessels may show necrotic and proliferative changes; it is stressed that these changes are not attributable either to chronic passive congestion or to superimposed infections. The so-called " Masson bodies " are the result of organization of the intra-alveolar fibrinous exudate when the alveoli do not undergo necrosis. The diagnosis of rheumatic pneumonitis may frequently be difficult owing to the paucity of physical signs. The condition does not respond to digitalis or antibiotics, but in a few cases may improve with salicylate therapy. In differential diagnosis, pulmonary infarction, lobar pneumonia, and bronchopneumonia can readily be distinguished. *J. Mester.*

Relation between Chorea and Acute Rheumatism. (Contributo alla conoscenza dei rapporti tra chorea minor e infezione reumatica.) POPPI, A. (1952). *Reumatismo*, **4**, 242. 5 figs, 28 refs.

The author points out that although there is no specific test for the presence or absence of rheumatic infection, the antistreptolysin-O titre of the serum indicates quantitatively the degree of previous streptococcal infection. Thus if the titre were higher in cases of uncomplicated chorea than in normal subjects, this would be supporting evidence of a rheumatic basis. At the Rheumatism Centre of the University of Bologna three groups of children were examined. Each group contained 55 children similarly distributed as to age and sex, and comprised cases of (1) " pure " chorea, (2) chorea with rheumatic manifestations, (3) rheumatism without chorea. A titre of more than 400 units was taken to indicate previous infection with haemolytic streptococci, such titres being found in normal children in 6 per cent. of cases. A titre of more than 400 units was found in 48 per cent. of Group (1), in 73 per cent. of Group (2), and in 70 per cent. of Group (3), these figures being based on the mean of the last and first titres estimated in each case. The titres in cases of pure chorea never achieved the levels found in the other groups, but the author notes that the rise in titre followed the same pattern in all three groups. There is therefore strong presumptive evidence that chorea is in some way related to rheumatism, although these observations provide no definite proof of the existence of such a relationship.

The gain in weight during the course of an attack of pure chorea was far greater than in any other rheumatic episode, and the blood pressure is higher in pure chorea than in other rheumatic diseases. It is suggested that in some subjects the response to streptococcal infection is limited to the nervous system, with stimulation of the pituitary gland, a higher production of corticotrophin, and a consequent reduction in the formation of collagen.

J. G. Jamieson.

Cortisone in Acute Rheumatic Carditis. BOONE, J. A., and BEACH, M. W. (1952). *Sth. med. J. Bgham, Ala.*, **45**, 556. 1 ref.

Problems arising in the Treatment of Rheumatic Fever with Corticotrophin and Cortisone. (Problèmes posés par l'emploi de l'ACTH et de la cortisone dans le traitement de la maladie de Bouillaud.) COSTE, F., and OURY, M. (1952). *Thérapie*, **7**, 103. 11 refs.

Problem of Rheumatic Fever in Infancy and the Grave Consequences of not diagnosing the Disease. (El problema de la fiebre reumatica infantil y sus graves consecuencias por desconocimiento de la afeccion.) COSTA BERTANI, G. (1952). *Rev. argent. Reum.*, **16**, 271.

Medico-Social Study of 120 New Cases of Infantile Rheumatism. (Estudio medico-social en 120 nuevos casos de reumatismo infantil.) SUMAY, R. S. R. (1952). *Rev. argent. Reum.*, **17**, 10.

Study of 91 Children with Rheumatic Fever in the Gulf Coast Area of Texas. LEBUS, H. E., and PANOS, T. C. (1952). *Tex. Rep. Biol. Med.*, **10**, 45. 2 figs, 11 refs.

Reactions of the Microglia of the Central Nervous System in Cases of Acute Rheumatism. (Contribution a l'étude des réactions de la micrologie du système nerveux central chez les malades atteints de rhumatisme aigu.) COSTERO, I. (1952). *Arch. Mal. Coeur*, **45**, 143. 4 figs, 11 refs.

Morbid Anatomy of Rheumatic Valvulitis. (Die anatomische Stellung der rheumatischen Herzklappenerkrankung.) BÖHMIG, R. (1952). *Z. Rheumaforsch.*, **11**, 92. 11 refs.

Pregnancy following Rheumatic Fever. JACOBSSON, E. (1952). *Acta obstet. gynec. scand.*, **31**, 471. 10 refs.

Present State of Knowledge concerning Pathogenesis and Treatment of Rheumatic Fever. MCCARTHY, M. (1952). *Bull. N.Y. Acad. Med.*, **28**, 307. 1 fig., 17 refs.

Epidemiology and Prevention of Rheumatic Fever. RAMMELKAMP, C. H., WANNAMAKER, L. W., and DENNY, F. W. (1952). *Bull. N.Y. Acad. Med.*, **28**, 321. 2 figs, 26 refs.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Rehabilitation of Hand Function in Rheumatoid Arthritis. ROSE, D. L., and KENDELL, H. W. (1952). *J. Amer. med. Ass.*, **148**, 1408. 7 figs, 26 refs.

The authors discuss the causation of the hand deformities characteristic of rheumatoid arthritis, taking the view that ulnar deviation is the result of an imbalance between the dorsal and palmar interosseus muscles, the fusiform palmar interossei having, under conditions of

chronic strain, a relative advantage over the bipennate dorsal muscles. They also consider that metacarpo-phalangeal-flexion and interphalangeal-extension deformities are due to excessive " splinting " of painful interphalangeal joints by the lumbrical muscles.

They outline a programme for rehabilitation of function of the hand which they have used in nine cases. Correction of the metacarpo-phalangeal deformity and ulnar deviation is attempted by active and passive movements of the hand on a smooth surface moistened with soapsuds or glycerine (the hand prints thus formed also give a rough indication of progress). The interphalangeal deformities are treated by exercises involving the use of a conical object (rather than the traditional tennis-ball, which is condemned). They also use a cotton glove to which hooks and eyes and rubber bands are fastened in such a way as to correct the ulnar deviation and, to some extent, the metacarpo-phalangeal subluxation.

In addition to these devices, and to a simple exercise regimen, they consider certain supportive measures of importance. Corticotrophin (ACTH) and cortisone have been used for brief periods, particularly when the exercise programme was being intensified. Procaine given orally has been used, and has been shown to have definite analgesic properties without any effect on eosinophilia or on the erythrocyte sedimentation rate. Lastly, the negative nitrogen balance found in rheumatoid arthritis has been countered by the administration of supplementary protein.

The authors emphasize that rehabilitation measures of this sort must remain simple so that the patient can carry them out without continuous supervision; the patient should also be warned not to expect immediate dramatic benefit. Critical appraisal will only be possible after long periods of observation. *B. E. W. Mace.*

Radiological Features of Rheumatoid Arthritis. FLETCHER, D. E., and ROWLEY, K. A. (1952). *Brit. J. Radiol.*, **25**, 282. 17 figs, 24 refs.

The clinical diagnosis of rheumatoid arthritis is fairly easy in the majority of cases, but the condition may be confused with subacute rheumatism, gout, Raynaud's disease, or polyarticular osteo-arthritis. Generalized bone diseases, such as hyperparathyroidism and osteomalacia, have been mistaken for rheumatoid arthritis.

The authors, who have examined radiographs taken in 200 cases of rheumatoid arthritis at Manchester Royal Infirmary, found that the incidence of the disease was highest in the age group 40-50 years, with a sex ratio of two females to one male. In most cases there was radiological evidence of the disease within 3 to 6 months of onset. In general the changes seen radiologically were bone erosions; joint changes, consisting of alterations in width of the space, subluxation, and ankylosis; osteoporosis and so-called secondary osteo-arthritis; and soft-tissue swellings. The incidence of local lesions was highest in the feet, especially in the 5th metatarso-phalangeal joint, many enlarged radiographs showing an apparent splitting of the articular cortex and an irregular saw-toothed contour. The authors point out that exposure should be made for the region of the metatarso-phalangeal joints and not for the foot as a whole. The authors' technique of enlargement is described. This is too involved for routine application but they recommend that for " the radiography of the extremities fine-grain industrial film should be used and processed for a reduced time in ordinary *x*-ray developer to obtain better detail ".

[This informative article is well worth reading.]

Geo. Vilvandré.

Rheumatoid Arthritis and Trauma. [In English.] EDSTRÖM, G. (1952). *Acta med. scand.*, **142**, 11. Bibl.

During the period 1941-50, 2,034 cases of rheumatoid arthritis were treated at the University Hospital of Lund, Sweden, and in 72 of these cases trauma was found to have occurred in close relation to the onset of the disease. The author presents a critical study of these cases, giving a short clinical note on each, and discusses fully the possible place of trauma in the aetiology of rheumatoid arthritis. The negative findings of Jonsson and Berglund (*Nord. Med.*, 1949, **41**, 7) in a similar series of cases may, it is suggested, be attributed to their adoption of very strict and rigid conditions to be fulfilled before the role of trauma in the aetiology could be accepted, and it is pointed out that even so they found a history of trauma within 12 months of the onset in eleven out of 1,669 cases, and were able to reject the possibility of an aetiological connexion in all but one of these only by attaching importance to a history of possible infection. As this hypercritical attitude was probably due to the apparent improbability of a traumatic cause, the conclusions which may be drawn from recent animal experiments are carefully examined, especially in relation to Selye's concept of " adaptation diseases ", among which he places rheumatoid arthritis.

In five of the author's 72 cases there was a history of a previous attack of arthritis (which in three occurred many years earlier), while in three cases an infective process was possibly related to the onset. His final conclusion is that trauma may be of aetiological importance, but that in comparison with other factors it appears to play a minor role. [The whole article is worthy of study in detail.] *C. W. Buckley.*

Pituitary Implantation in Rheumatoid Arthritis. (Hypophyseimplantation ved polyarthritis chronica.) WASSERMAN, K. (1952). *Ugeskr. Laeg.*, **114**, 535. 2 refs.

The author reports the treatment of 53 cases of moderate or severe rheumatoid arthritis by the intramuscular implantation of calf pituitary tissue at the Aalborg City Hospital. The stay in hospital was one week. Of the 53 patients, sixteen were men and 37 women, and 65 per cent. were aged between 40 and 60. Nine patients received one implant, 39 two, and five three implants. All patients were in an acute stage of their illness, with erythrocyte sedimentation rates ranging from 1 to 138 mm. (mean 44 mm.) in one hour. The condition was classified as slight in one case, moderate in eighteen, and severe in 34. The results were assessed from objective examination of the joints, from the patient's use of analgesics, and from his ability to return to work.

Of the 41 patients followed up, 37 reported subjective

improvement, which was not always confirmed by the objective findings. In none did the condition deteriorate. The degree of response was not related to age or sex, but treatment was significantly more effective in the moderate than in the severe cases. Relapse occurred in 28 cases after periods ranging from 1 week to 9 months (mean 3 months). Improvement in the remaining nine cases was still evident 8 to 12 months after implantation. In eleven of seventeen patients with arthritis of less than 7 years' duration improvement lasted 4 months or longer, but in only five of 24 patients whose illness had lasted longer than 7 years was improvement maintained for this period. The treatment usually became effective within one week. The erythrocyte sedimentation rate fell slowly in most cases, though in a few cases a rapid and dramatic fall was observed. One patient developed urticaria accompanied by a high temperature. A marked increase of pre-existing albuminuria was observed in one case, but in another the degree of albuminuria was unaffected. No effect on blood pressure was observed.

The author comes to the conclusion that in view of the severity of the condition in most of the patients the results are an astonishing improvement on those of the usual methods of treatment. Pituitary implantation can be carried out quickly and cheaply, and its effect is similar to that of corticotrophin, though acting more slowly and lasting longer. A significant disproportion was noted, between the hormone content of the implant and its effect, which has been ascribed to " transient hormonal shock ". *E. S. Fountain.*

Electromyogram in Rheumatoid Arthritis. MUELLER, E. E., and MEAD, S. (1952). *Amer. J. phys. Med.*, **31**, 67. 4 figs, 16 refs.

The authors have investigated the electromyogram in 25 cases of rheumatoid arthritis at the Washington University School of Medicine, St. Louis, Missouri. Using this method of investigation they set out to assess the theory that muscle spasm is a cause of the muscle atrophy associated with the disease. The 25 patients, nine male and sixteen female, whose ages ranged from 4½ to 73 years, had been suffering from rheumatoid arthritis for periods varying from 1 to 22 years. A group of 25 uncomplicated orthopaedic cases was taken as a control. The apparatus used (not described in detail) consisted of suitable amplifiers with photographic recording from cathode-ray oscilloscopes. The action potentials were detected by the use of both surface and co-axial needle electrodes.

It was found that no spontaneous activity could be detected with the subject at rest, provided that the position of the muscle tested was carefully adjusted. (Exceptions were found only in cases where concurrent neurological disorders existed.) The recordings during voluntary activity showed essentially a reduction in amplitude of the normal interference pattern, as is found in debilitating diseases; occasionally, isolated potentials of the myopathic type were observed. A few patients (number unstated) were examined before, during, and after treatment with cortisone and corticotrophin. No change in the action potentials was observed as a result of treatment with these drugs, except that it was found to be easier to position the patient to secure electrical inactivity of a muscle at rest.

The discussion is mainly concerned with the evaluation of theories regarding the cause of muscle weakness and atrophy in rheumatoid arthritis, and the authors consider that their results are compatible with the theory that the atrophy is due to a central inhibitory state in the spinal cord mediated by the pain impulses from the lesions.

[The authors offer no positive evidence in support of this theory, but their results show that in their small series there was no evidence of disturbance of the normal mechanism of neuromuscular transmission in rheumatoid arthritis, and they found no unequivocal evidence of muscle spasm in any case.] *Kenneth Taylor.*

Placental Serum Therapy for Rheumatoid Arthritis. ARONSON, W., LEVY, F., BESEN, L. J., and LEFF, M. (1952). *Amer. J. med. Sci.*, **223**, 144. 5 refs.

From the Morrisania City Hospital, Bronx, New York, the authors report the results of a trial of the use of placental serum in 33 cases of active rheumatoid arthritis and two cases of Marie-Strümpell disease. The apparatus and technique for obtaining placental serum is described and illustrated. Serum was found to give better results than plasma; treatment consisted of a bi-weekly injection of 10 ml. of the serum intramuscularly. The patients were all ambulatory, and were assessed in reference to severity of the condition, function, and response to treatment by the standards of the New York Rheumatism Association. Controls were made by changing the injection for a period to pooled " non-pregnant " plasma; it is stated that there was an " absence of improvement with the non-pregnant plasma ".

Treatment has to be continued " for a long time " (20 or more weeks). Response was not spectacularly rapid but gradual, and in nine cases an apparent clinical remission was induced. Relapses occurred, but were generally responsive to further treatment. Improvement was shown by moderate reduction of subjective stiffness and pain, of pain on movement, and of articular tenderness, and by slight reduction of joint swelling. There was improvement in muscle strength and joint function, generally with better appetite and sleep, a sense of well-being, and a lowered sedimentation rate. Two case histories are reported, and the general results are summarized in a table which shows a Grade 2 response in 23 patients (65 per cent.) and no improvement in four (12 per cent.). Results were better in the younger patients and in cases of shorter duration. *Harry Coke.*

Use of Red Cell Mass in Rheumatoid Disease. GARRY, M. W. (1952). *Amer. J. med. Sci.*, **223**, 642. 12 refs.

It has long been recognized that anaemia is closely associated with rheumatoid arthritis, and may be of the normocytic or of the microcytic hypochromic variety. Experience has shown it to be highly refractory to iron therapy. On the assumption that blood dilution may be responsible for the production of this anaemia, the author has determined the blood and plasma volume in a series of 25 patients with rheumatoid arthritis, together with a control series of normal subjects of similar age, at the U.S. Veterans Hospital, Wood, Wisconsin.

It was found that there was a substantial increase in the plasma volume in the patients with rheumatoid arthritis as compared with the control series, and it appeared that this was sufficient to account for their anaemia. Transfusions of the erythrocytes from a total of 6 to 10 pints (3·4 to 5·7 litres) of blood restored the normal erythrocyte-plasma relationship, and this form of therapy is regarded by the author as a valuable measure in severely anaemic cases of rheumatoid arthritis provided it is repeated with sufficient frequency and in the absence of transfusion reactions. *W. S. C. Copeman.*

Rheumatoid Granulomatous Nodules as Destructive Lesions of Vertebrae. BAGGENSTOSS, A. H., BICKEL, W. H., and WARD, L. E. (1952). *J. Bone Jt Surg.*, **34A**, 601. 4 figs, 13 refs.

A patient with rheumatoid arthritis and a subcutaneous nodule had limitation of movement of the back; radiographs of the spine showed osteoporosis and collapse of the twelfth thoracic vertebra. Substernal pain, which the patient had previously noted on exertion, reappeared, and the patient died from myocardial infarction. Necropsy revealed pericarditis of the rheumatoid type with effusion, rheumatoid nodules at the base of the mitral valve and at the apex of the left ventricle, and areas of myocardial necrosis and fibrosis due to partial coronary obstruction by atheroma. Histologically, rheumatoid changes were seen in the joints, and the twelfth thoracic and third lumbar vertebrae showed invasion by granulomatous tissue, which in places resembled a rheumatoid nodule with palisading. [The illustrations, which accompany the article, of the histological appearances are excellent.]

In three other patients, in whom a diagnosis of ankylosing spondylitis had been made, destructive lesions in the anterior part of some of the lower thoracic or upper lumbar vertebrae were found. The authors, being unable to find any other cause, diagnose these lesions as rheumatoid granulomatous nodules: no pathological material was obtained.

[In spondylitis ankylopoietica nodule formation does not occur.] *E. G. L. Bywaters.*

Preliminary Report of the Anti-rheumatic Action of Heparin and Paritol-C in Gout and Rheumatoid Arthritis. HOWE, G. W., ARMBRUST, C. A., LEVY, M. D., and WAGNER, E. L. (1952). *Amer. J. med. Sci.*, **223**, 258. 15 refs.

The anti-rheumatic effects of treatment with heparin and with " Paritol-C " (a polysulphuric acid ester of polyanhydromannuronic acid) were studied in five cases of " acute, non-tophaceous, gouty arthritis ", six cases of active subacute rheumatoid arthritis, and two cases of acute non-specific arthritis. Heparin was given subcutaneously in doses of 200 and 300 mg. every 12 hours; Paritol was administered intravenously, 3 to 4 mg. per kg. body weight being given in 5 to 10 per cent. solution every 12 to 24 hours. The duration of the treatment depended on the response.

In all five cases of gouty arthritis, one of which was treated with heparin and four with Paritol, a complete remission of symptoms occurred within 36 to 96 hours. No significant change was observed, however, in the serum uric acid level or erythrocyte sedimentation rate during or after the treatment. A similarly complete remission of symptoms was obtained in the two cases of non-specific arthritis, which were treated with Paritol. The response in rheumatoid arthritis was less dramatic: only in one case out of six was a complete remission obtained, and in one case no improvement was observed.

[The anti-rheumatic effect of anticoagulants had been described before. The point of interest is the inclusion of five cases of gouty arthritis.] *A. Swan.*

Treatment of Rheumatoid Arthritis with Nitrogen Mustard. Preliminary Report. JIMÉNEZ DÍAZ, C., LÓPEZ GARCIA, E., MERCHANTE, A., and PERIANES, J. (1951). *J. Amer. med. Ass.*, **147**, 1418. 7 refs.

Certain similarities between the actions of cortisone and nitrogen mustard led to a trial of the latter in the treatment of nine patients suffering from rheumatoid arthritis at the Medical Clinic of the University of Madrid. The results are described as spectacular, pain and limitation of movement disappearing after the second injection. The authors hope soon to report a larger series of cases. *D. P. Nicholson.*

Experience with Nitrogen Mustard in the Treatment of Rheumatoid Arthritis. The Myelogram in this Condition. (Experiencia con metil-bis-beta-cloroetyl-amina en la artritis reumatoide. El mielograma en la artritis reumatoide.) LOSADA, M., ETCHEVERRY, L. R., DAIBER, A., and GUZMAN, C. (1952). *Rev. med. Chile*, **80**, 164. 8 refs.

Following Jiménez Díaz's report on nitrogen mustard in rheumatoid arthritis, the authors subjected ten patients to treatment with methyl-bis-β-chlorethylamide. [Jiménez Díaz used methyl-tri-β-chlorethylamide.]

Of these patients, nine were suffering from typical rheumatoid arthritis and one had Felty's syndrome; seven of them were women and three were men, and the average duration of the condition was over 4 years. The nitrogen mustard was used in the form of " Dichloren " or " Mechloretamine "; the total dose ranged from 11 to 16 mg., single doses being from 3 to 6 mg. according to the patient's general condition. Most of the patients had had previous treatment with gold and cortisone. It is stated that seven of the patients showed some improvement, both subjective and objective, but that this was transient in character. The authors' conclusion is that the clinical improvement and improvement in the erythrocyte sedimentation rate were not greater than in spontaneous remissions. They could not confirm Jiménez Díaz's observations regarding the reduction in eosinophils and lymphocytes in the peripheral blood.

An investigation was also made of the changes in the bone marrow of eleven patients suffering from rheumatoid arthritis; in all the marrow cases the picture was normoblastic or slightly hyperplastic. In the erythrocytic series there was a 20 to 30 per cent. increase in the erythroblasts with a normal reticulocyte count; in the case of Felty's

syndrome there was a 45 per cent. increase in erythroblasts and a reticulocytosis of 11 per cent. In the granulocyte series the majority of patients showed a 30 per cent. increase in stab-form neutrophil leucocytes. Eosinophils showed a moderate increase up to 8·4 per cent., reaching 13·5 per cent. in one case, but as the authors rightly point out the effect of previous treatment should be borne in mind. The monocytes and lymphocytes were within normal limits. The megakaryocytic counts were normal or slightly increased, with the exception of the case of Felty's syndrome in which no megakaryocytes were found and only scanty platelets. Plasma cells were definitely increased (by 3·5 to 6 per cent.) in four cases, and in five cases there was an increase in reticulocytes. Nitrogen mustard treatment did not cause any appreciable changes in the morphology of the marrow cells. *J. Mester.*

Effect of Cation Exchange Resins in Preventing Water Retention during the Treatment of Rheumatism with Cortisone. (Azione antiedemigena delle resine a scambio di cationi nei reumatici sottoposti a cura cortisinica.) LUCHERINI, T., and VENIALI, G. (1952). *Minerva med., Torino*, **43**, 821. 4 refs.

Disturbance of electrolyte balance is one of the undesirable side-effects of protracted treatment with cortisone, which leads to sodium chloride retention and potassium loss, thus producing oedema, increase in weight and polydipsia, accompanied by hypochloraemic alkalosis, muscular weakness, and changes in the electrocardiogram. Treatment with mercurial diuretics, ammonium chloride, and low-chloride and high-potassium diet, has proved unsatisfactory.

Cation exchange resins have been found effective in preventing water retention in hepatic cirrhosis, Cushing's syndrome, and nephrosis. These resins have a complex structure which enables them to take up one ion, such as potassium, in exchange for another, such as ammonium. The authors used a mixture containing 59 per cent. of a carbosilicate resin, 29 per cent. of its potassium salt, and 12 per cent. of a polyaminic-formaldehyde anion exchange resin (" Carboresin "). This mixture is reputed to prevent the danger of hypopotassaemia, and especially the unwelcome acidosis caused by the liberation of chlorides, the anion-exchange part of the mixture eliminating the danger of low alkaline reserve. The mixture was given orally in doses of 15 g. daily for 5 to 7 days, and repeated if necessary. In patients with concurrent prolonged cortisone treatment the same amount was given for 10 days, and then every 3 days during cortisone administration.

In oedematous patients this treatment produced an immediate and considerable increase of diuresis, with concomitant loss of weight. In patients who received the treatment from the beginning of cortisone therapy there was no disturbance of electrolyte metabolism and no sign of oedema. The dose of 15 g. daily is much lower than the 40 or 50 g. used in hepatic cirrhosis, but was usually sufficient, and was well tolerated by patients having a prolonged course of cortisone (up to 50 mg. daily). The blood potassium level was not significantly influenced. *V. C. Medvei.*

ACTH in the Treatment of Juvenile Rheumatoid Arthritis. [In English.] VESTERDAL, J., REMVIG, O., and SPRECHLER, M. (1952). *Acta paediatr., Stockh.*, **41**, 145. 4 figs, 9 refs.

A description is given of the treatment at the National Hospital, Copenhagen, of seven children suffering from juvenile rheumatoid arthritis with daily doses of 24 i.u. of corticotrophin given for 6 to 14 days and then gradually reduced. A good effect was seen in most instances, but on cessation of treatment symptoms tended to recur. It is concluded that corticotrophin is indicated for those who are developing deformities, or where deformities are present without osseous ankylosis. *D. P. Nicholson.*

Cortisone and Gold Therapy in Chronic Rheumatoid Arthritis. THOMPSON, H. E., and ROWE, H. J. (1952). *Ann. intern. Med.*, **36**, 992. 7 refs.

To determine whether cortisone and gold given concurrently were more effective than when either drug was given separately, three groups of patients with rheumatoid arthritis were studied:

(1) To eight patients who were already receiving gold injections cortisone was given in addition for 6 to 18 months. The response to cortisone was good in all cases, but all relapsed on its withdrawal and it is evident that the addition of the hormone did not increase the effect of gold.

(2) To thirteen patients both drugs were given concurrently for similar periods, starting simultaneously. In three of these a significant remission occurred and was maintained on withdrawal of cortisone, in one case for 229 days. Dermatitis occurred in only one of the seven patients who had had previous reactions to gold. The functional capacity increased in all these patients.

(3) Cortisone alone was given to 42 patients, with a consequent increase in functional capacity; in one case this was maintained on withdrawal of cortisone.

The authors conclude that a combination of gold and cortisone is superior to cortisone alone in the treatment of rheumatoid arthritis, and that it elicits an excellent therapeutic response with an increase in functional capacity and a complete remission in some cases. In patients who receive only moderate benefit from gold alone, however, the addition of cortisone does not produce an arrest of the disease. [As they rightly state, the number of patients in each group was not sufficient for statistical analysis and their conclusions must be regarded as provisional.] *Oswald Savage.*

Haematological Changes in Patients with Rheumatoid Arthritis Treated with ACTH or Cortisone. (Modifications hématologiques observées chez des malades atteints de polyarthrite chronique évolutive traités par l'ACTH ou la cortisone.) LAYANI, F., ASCHKENASY, A., PAUWELS, R., and PUYO, G. (1952). *Sem. Hôp. Paris*, **28**, 1119. 3 figs, 20 refs.

In spite of the extensive literature which has accumulated on the subject of cortisone and corticotrophin (ACTH), the specific action of these substances on the blood picture of chronic rheumatoid arthritis does not emerge very clearly. The present study was carried out

at the Hôtel-Dieu, Paris, on 22 patients with typical rheumatoid arthritis who had been given no treatment for a week before the start of the investigations reported. They were then given a minimum period of 15 days' treatment with one of these hormones.

Both substances produced a moderate increase in the erythrocyte count and in the haemoglobin content of the blood. The increase in the haematocrit reading was more marked in most cases, the erythrocyte volume being apparently increased as the result of intracellular water retention. Both substances increased the polymorphonuclear leucocyte count, and at the same time produced a fall in the eosinophil count, which was more marked after ACTH than after cortisone. The fall in the E.S.R. and in the serum content of both fibrinogen and gamma globulin was also more rapid and more marked after ACTH. *W. S. C. Copeman.*

Effect of Cortone and ACTH on the Histopathologic Lesions of Rheumatoid Arthritis. NORCROSS, B. M., LOCKIE, L. M., CONSTANTINE, A. G., TALBOT, J. H., and STEIN, R. H. (1952). *Ann. intern. Med.*, **36**, 751. 10 figs, 13 refs.

A histological study was made at the Buffalo General Hospital, New York, of tissue from 27 patients with rheumatoid arthritis, from two with rheumatoid spondylitis, and from one with rheumatoid arthritis associated with psoriasis, the aim being to demonstrate the changes which occur in the lesions after the administration of cortisone and ACTH (corticotrophin). Muscle biopsy was performed on all thirty patients, nodule biopsy on twelve (on three both before and after hormone therapy), and synovial-membrane biopsy on two before and after therapy. The muscle lesions were divided into:

(1) inflammatory nodules, Grades 1 to 3 (based on the number of lymphocytes in the cell collections);

(2) degenerative lesions, Grades 1 to 3 (based on the degree of muscle atrophy, fibre swelling, and increase of sarcolemmal nuclei).

Only patients with Grade-2 lesions in both categories were used in assessing the effect of the hormones. Such lesions were present in eleven patients, and in eight of them there was a definite improvement, the inflammatory nodules disappearing in five cases and showing regression in three; the degenerative lesions also improved, but to a lesser extent. The subcutaneous nodules altered considerably, the smaller nodules disappearing and the larger nodules becoming smaller; in two out of three cases, comparison of nodules removed before and during therapy showed a definite histological change, the palisade layer having practically disappeared and the round-cell infiltration being diminished. The authors remark, however, that this alteration may represent a stage in the evolution of the lesion rather than a specific effect of the hormone. The synovial membrane appeared to become normal in both the patients undergoing biopsy; on gross inspection and histologically there was a marked decrease in vascularity and oedema, with reduction of cellular reaction. There was no delay in wound healing in any of the patients.

[The synovial membrane illustrated in one patient shows a striking change after 16 days of ACTH therapy (probably greater than can be accounted for by variation from site to site within the knee-joint). No details, however, are given of dosage, of any other criteria of response, or of the time at which the biopsies were performed following the start of therapy except in the five cases used for illustrations.] *E. G. L. Bywaters.*

Compound F used Orally in Patients with Rheumatoid Arthritis. BOLAND, E. W., and HEADLEY, N. E. (1952). *J. Amer. med. Ass.*, **148**, 981. 23 refs.

The only steroid compound which has so far been found to exert a therapeutic effect comparable to that of cortisone is Kendall's Compound F (17-hydroxycorticosterone; hydrocortisone), which is at present, unfortunately, more expensive to produce than cortisone itself. The authors administered this substance in its free form (as opposed to the acetate) to fifteen patients with chronic rheumatoid arthritis. They found, as they expected, that the activity of the disease was suppressed in highly effective fashion, and that short-term administration maintained excellent control of the rheumatic manifestations. Suppression occurred more rapidly and with smaller doses than was the case when cortisone was used, and the erythrocyte sedimentation rate fell to within normal limits sooner. Free Compound F was also found to be consistently more effective in maintaining anti-rheumatic control, the required dosage of cortisone acetate being 1·43 to 1·7 times as great, the average ratio being 1·56 : 1. Thus the potency of free Compound F would appear to be roughly 50 per cent. greater than that of cortisone acetate.

This greater potency did not appear to be accompanied by a corresponding increase in tendency to produce adverse side-effects. Indeed, in several patients minor side-effects which had been present during the administration of cortisone disappeared or diminished when the treatment was changed to equally effective doses of free Compound F. Free Compound F appeared to be similarly superior to Compound F acetate in potency. The therapeutic evaluation of free Compound F must, however, await a final assessment of the results of long-term treatment studies. *W. S. C. Copeman.*

Treatment of Rheumatoid Arthritis with Butazolidin. CURRIE, J. P. (1952). *Lancet*, **2**, 15. 4 refs.

It has been observed that the relief of pain in rheumatoid arthritis was much greater when amidopyrine was administered in the injectable form as " Irgapyrin " than when the equivalent blood concentration was obtained by its administration by mouth. In addition " Irgapyrin " appeared to reduce joint swelling. This paper describes a carefully controlled investigation of the value of the solvent used in the preparation of " Irgapyrin ", namely, Butazolidin (1:2-diphenyl-3:5-dioxo-4-*n*-butylpyrazolidine), a substance of low toxicity. Its pharmacology is discussed.

At Glasgow Royal Infirmary 81 cases of rheumatoid arthritis were selected by the usual diagnostic criteria [although their plasma viscosity should have been raised

and not reduced]. They were given daily intramuscular injections of 1 g. Butazolidin in a 20 per cent. solution and of normal saline for 10 days each. The cases were assessed before treatment and at 10 and 20 days after. Of the 81 patients, 77 showed subjective improvement with lessened pain and freer movement, and in 24 cases there was measurable objective evidence of improvement. It is considered highly significant that 30 per cent. of cases of rheumatoid arthritis should show objective improvement in the short space of 3 weeks. No electrolyte shift was observed nor any change in the eosinophil count or 17-ketosteroid excretion. The author concludes by claiming that " as an anodyne in cases of rheumatoid arthritis, Butazolidin is quite exceptionally effective ". *Harry Coke.*

Plasma and Red Cell Catalase in Rheumatoid Arthritis. JEFFREY, M. R. (1952). *J. Lab. clin. Med.*, **39**, 390. 4 refs.

Serum Iron Content in Rheumatoid Arthritis. (Das Serumeisen bei der chronischen Polyarthritis.) FERSTL, A., and SCHMID, J. (1952). *Wien. Z. inn. Med.*, **33**, 141. 7 figs, 37 refs.

Significance of the Agglutination of Sensitized Sheep's Erythrocytes in Rheumatoid Arthritis. (Die Bedeutung der Haemagglutination sensibiliserter Schaferythrozyten bei chronischer Polyarthritis.) EHRMANN, G., FERSTL, A., NEUMAYR, A., and SCHMID, J. (1952). *Wien. Z. inn. Med.*, **33**, 81. 2 figs, bibl.

Agglutination of Sensitized Sheep's Erythrocyte by the Serum of Patients with Rheumatoid Arthritis. (Aglutinacion de los globulos rojos de carnero sensibilizados por el suero sanguineo de los enfermos de artritis reumatoide.) ALÉS REINLEIN, J. M., and ARJONA TRIGUEROS, E. (1952). *Rev. clín. esp.*, **44**, 169. 16 refs.

Plasma Fibrinogen and the Sedimentation Rate in Rheumatoid Arthritis, and their Response to the Administration of Cortisone and Adrenocorticotropic Hormone (ACTH). FLETCHER, A. A., DAUPHINEE, J. A., and OGRYSLO, M. A. (1952). *J. clin. Invest.*, **31**, 561. 8 figs, 25 refs.

Nitrogen Mustard in Rheumatoid Arthritis. (L'azoiprite nell'artrite reumatoide.) CONESTABILE, E., NATALE, P., and CERIMELE, E. (1952). *Policlinico. Prat.*, **59**, 333. 7 figs, 9 refs.

Rheumatoid Arthritis: Sanocrysin Treatment and Prognosis. SNORRASON, E. (1952). *Acta med. scand.*, **142**, 249. 2 figs, 18 refs.

Butazolidin in Rheumatoid Disorders. A Preliminary Report. SMITH, C. H., and KUNZ, H. G. (1952). *J. med. Soc. N.J.*, **49**, 306.

Results of Treatment of Rheumatoid Arthritis with Phosphocrysol. (Risultati clinici nella cura della poliartrite cronica primaria ottenuti con il Fosfocrisolo.) RIZZI, M. (1952). *Minerva med.*, **1**, 1177. 5 figs, 13 refs.

Circulation and Elimination of Organic Copper Compounds used in the Treatment of Inflammatory Rheumatism. (Circulation et élimination des composés organo-cupriques utilisés dans le traitement des rhumatismes inflammatoires.) TRAVERSE, P. M. DE, DEPRAITÈRE, R., and JACQUELINE, F. (1952). *Thérapie*, **7**, 148. 1 ref.

Clinical Evaluation of Chloroethylamine in the Treatment of Rheumatoid Arthritis. (Valutazione clinica del trattamento della poliartrite cronica primaria con cloroetilamine.) GALLI, T., and MANNETTI, C. (1952). *Reumatismo*, **4**, 289. 5 figs, bibl.

Effect of Contrast Baths on the Vasomotor Response of Rheumatoid Arthritis Patients. FRICKE, F. J., and GERSTEN, J. W. (1952). *Arch. phys. Med.*, **33**, 210. 3 figs, 10 refs.

Clinical and Radiological Aspects of the Involvement of the Hip Joint in Rheumatoid Arthritis and Ankylosing Spondylitis. (Aspects cliniques et radiologiques de l'atteinte de la hanche dans la polyarthrite chronique évolutive et la spondylarthrite ankylosante.) FORESTIER, J. (1952). *Rhumatologie*, **2**, 49. 5 figs, 2 refs.

Involvement of the Hepatic Parenchyma in Felty's Syndrome. (Über Leberparenchymaffektion beim Felty-Syndrom.) SCHNEIDERBAUR, A., and SAMEC, V. (1952). *Wein. med. Wschr.*, **102**, 585. 33 refs.

A Case of Rheumatoid Arthritis in an Acromegalic Patient. (A propos d'un cas de polyarthrite chronique évolutive chez une patiente acromégalique.) RIZZI, M., and SUTER, K. (1952). *Rhumatologie*, **3**, 110. 5 refs.

Deaths from Rheumatoid Arthritis, 1940-1949. BROOKE, E. M. (1952). *Monthly Bull. Minist. Hlth (Lond.)*, **11**, 57. 2 figs.

(Osteo-Arthritis)

Generalized Osteo-arthritis and Heberden's Nodes. KELLGREN, J. H., and MOORE, R. (1952). *Brit. med. J.*, **1**, 181. 9 figs, 16 refs.

From a study of 391 cases of osteo-arthritis the authors have defined a clinical entity which they term " primary generalized osteo-arthritis ". This entity occurs most frequently in middle-aged women, and is characterized by a distinct pattern of joint involvement which they describe in detail. Each affected joint passes through an initial painful and more or less acute arthritic phase, and since this process is not confined to the terminal phalanges

of the fingers (where it is well recognized) there is a danger of the condition being mistakenly diagnosed as rheumatoid arthritis. The other clinical and radiological features which distinguish this syndrome are well described.

The authors regard generalized osteo-arthritis as a constitutional disease resulting from an inherited defect similar to that which gives rise to " idiopathic " Heberden's nodes. They consider that much can be done to help sufferers from this disease by the proper management of their complaints, although there is no specific treatment available. *W. S. C. Copeman.*

Peripheral Ischaemia as the Basis of Joint Disease. (Serial Angiography of the Periarticular Blood Vessels.) LEB, A. (1952). *Brit. J. Radiol.*, **25**, 140. 5 figs, 6 refs.

The author describes a technique for peripheral angiography of the upper limb in cases of osteo-arthritis of the hand, as used at the Central Roentgen Institute, Graz. The brachial artery is exposed at the elbow and 6 ml. of thorotrast injected. (This medium is preferred to the organic iodine compounds, which cause spasm in the peripheral vessels.) The injection takes 2 or 3 seconds and the first radiograph is taken during the injection. Further films are taken at 5-second intervals for the first minute, and at 15- to 30-second intervals during the second minute.

The characteristic finding in osteo-arthritis is a reduction in arterial blood flow, the lumen of the digital arteries being reduced and venous stasis being present. The author considers that the peripheral vascular damage precedes the joint lesion and may be the cause of it.

D. E. Fletcher.

Preventive Treatment of Arthritis of the Hip. (Le traitement préventif de la coxarthrose.) GRABER-DUVERNAY, J. (1952). *Rhumatologie*, **2**, 67. 2 figs, 4 refs.

Functional Prognosis of Arthritis of the Hip. (Le pronostic fonctionnel de la coxarthrie.) FRANÇON, F. (1952). *Rhumatologie*, **2**, 62. 1 ref.

Thoracic and Anginal Pain in Cervical Osteo-arthritis. (Douleurs thoraciques et angineuses au cours de la cervicarthrose.) RAVAULT, P. P., VIGNON, G., and BRUEL, P. (1952). *Rev. Rhum.*, **19**, 320. 29 refs.

(Spondylitis)

Nontraumatic Cervical Dislocations in Rheumatoid Spondylitis. KORNBLUM, D., CLAYTON, M. L., and NASH, H. H. (1952). *J. Amer. med. Ass.*, **149**, 431. 6 figs, 11 refs.

The authors, from the Cushing Veterans Administration Hospital, Framingham, Massachusetts, report the cases of four patients suffering from ankylosing spondylitis who developed non-traumatic cervical dislocation. The onset was insidious, with pain in the neck and progressive development of rotation and flexion deformities. In two cases there was anterior subluxation of the atlas on the axis; one of these patients developed numbness and tingling in the arms and legs shortly before admission to hospital. The other two dislocations were of C 5 on C 6, and of C 6 on C 7 respectively. In one of the cases of atlanto-axial subluxation, the deformity appeared to be fixed, and head traction and other measures were unsuccessful in correcting it; in the other, treatment by continuous head traction for 6 weeks relieved the symptoms, and reduction was confirmed radiologically. In the case of subluxation of C 5 on C 6 reduction and relief of symptoms were also obtained by continuous head traction, while the fourth patient refused treatment.

The authors point out that hyperaemia, capsular distension, and ligamentous relaxation, such as may occur in active rheumatoid spondylitis, are important factors in the aetiology of these spontaneous cervical dislocations.

The desirability of surgical fusion of the involved segments of the spine is discussed. The advantage of such surgical treatment in preventing recurrence is obvious, but the poor general condition of the patient often makes operation risky; moreover, fusion of the affected joints may occur spontaneously in time. *C. E. Quin.*

Natural History of Ankylosing Spondylitis. (Sul nosografismo della spondilite anchilosante.) LUCHERINI, T., and CECCHI, E. (1952). *Reumatismo*, **4**, 125. 22 figs, bibl.

The authors report their observations on twelve cases of ankylosing spondylitis seen at the Rheumatism Centre of the University of Rome during 1951. The patients' ages varied between 20 and 76, and only one was female.

The cutaneous manifestations took the form of striae in four cases in the region of the knee, where a rheumatic lesion was consistently demonstrated; and in one case on the back, where they formed a herring-bone pattern radiating from the midline downwards and outwards; in five cases there was dilatation of the small cutaneous veins of the side of the chest wall, as has been reported a number of times by North American authors.

One patient had a generalized psoriasiform eruption, and the clinical picture deteriorated progressively.

Evidence of focal sepsis was demonstrated in a number of cases and in one case there was active pulmonary tuberculosis, but there was not thought to be any relationship between the tuberculosis and the spondylitis, except in so far as the former would tend to aggravate the latter.

Arthritis which was found in all cases of the series, usually took the form of a polyarthritis of the ankles, shoulders, knees, hips, elbows, and wrists, decreasing in that order and relatively much less frequent in the metacarpal and metatarsal joints. In all cases there was sacro-iliac arthritis.

The authors conclude that ankylosing spondylitis is not an infective inflammatory process (though the initial stimulus may be of an infective nature), but a particular proliferative process analogous in histological aspects to a special type of enchondroma of the intervertebral disk. In the present state of our knowledge it is their conviction

that there is no valid argument against classifying ankylosing spondylitis as a vertebral variety of rheumatoid arthritis. *Edgar J. Gatt.*

Rheumatoid Spondylitis. MYERSON, R. M. (1952). *Delaware St. med. J.*, **24**, 69. 5 refs.

Senile Ankylosing Vertebral Hyperostosis. (De l'hyperostose ankylosante vertébrale sénile.) OTT, V. R. (1952). *Rhumatologie*, **3**, 104. 4 figs, 6 refs.

Senile Ankylosing Hyperostosis of the Spine. (Zur Frage der "Senilen ankylosierenden Hyperostose der Wirbelsaule".) OTT, V. R. (1952). *Z. Rheumaforsch.*, **11**, 95. 6 figs, 7 refs.

Juxta-discal Bony Bridges. Macroscopic Study of a Specimen from a Case of Ankylosing Spondylitis. (Ponts osseux juxta-discaux. Étude macroscopique d'une pièce de spondylarthrite ankylosante.) JACQUELINE, F., and ROTES-QUÉROL, J. (1952). *Rev. Rhum.*, **19**, 445. 2 figs, 18 refs.

(Miscellaneous)

Observations on Weather-Sensitive Arthritis during Controlled Exposures to Low and High Atmospheric Pressures. JONES, H. L., and REEVES, E. (1952). *J. Aviat. Med.*, **23**, 77. 17 refs.

The effects on joint pain of repeated exposures to increased barometric pressures (up to half an atmosphere) in a high-pressure chamber were studied at the U.S. Naval Air Station, San Diego, in six subjects with chronic arthritis, all of whom claimed that the approach of bad weather caused an exacerbation of their joint symptoms. The subjects were exposed to varying pressure increases or to normal atmospheric pressure for periods of varying duration without knowing when changes were made, and recorded their subjective assessment of pain in a given joint at 5-minute intervals according to an arbitrary scale. Pain responses in two subjects (one with rheumatoid arthritis and one with traumatic osteo-arthritis) and possibly in a third (osteo-arthritis) suggested that exposure to a rise in barometric pressure of half an atmosphere for about one hour had a definite effect in decreasing pain. Joint pain was uninfluenced in the fourth patient, pain estimations in the remaining two were invalidated by psychological factors and multiple joint involvement. Further investigations along these lines are indicated, especially in view of the possible role of weather changes as "stressor" agents in the aetiology of rheumatic disease. *Ellis Dresner.*

Pathology of Pleonosteosis. (Zur Pathologie der Pleonosteose (Léri).) MATERNA, A. (1952). *Beitr. path. Anat.*, **112**, 112. 15 figs, 36 refs.

In 1922 Léri described a family in which three individuals (the father and two children) were affected with a condition manifested by dwarfism, irregular thickening of limb bones, and flexional deformities of the fingers. He gave the name "pléonostéose" (superfluous ossification) to the syndrome, which is now usually grouped with two other rare familial conditions, the Morquio-Brailsford syndrome, and the Pfaundler-Hurler syndrome (gargoylism), the entire group being known as the endochondral dysostoses or chondro-osteo dystrophies. The skeletal changes in the three types have certain similarities, but pleonosteosis shows a dominant mode of inheritance, while the other two are recessive. [British and American literature contains little reference to pleonosteosis; one article, however, by Watson-Jones (*J. Bone Jt Surg.*, 1949, **31B**, 560) directs attention to the soft tissue changes present in the condition, and gives a bibliography, mainly French, up to 1949.]

So far, descriptions of the chondro-osteo dystrophies have dealt chiefly with the clinical pattern and the observed radiographic changes, but little has been said concerning their underlying pathology or of the mechanism by which the genetic abnormality affects the developing skeleton. The present paper makes a start in this direction by putting on record the gross and microscopical bone changes found post mortem in a case of pleonosteosis studied in Czechoslovakia during the period of German occupation. Two brothers and their father were affected, but details were available for only one of the brothers who died at the age of 39 with infective hepatitis and old rheumatic carditis. His skeleton showed what are regarded as the characteristic changes of the condition. He was of short stature, with a conspicuously short neck; the large skull had a thickened vault and there was exaggerated growth of the facial bones. The spine showed thoracic kyphosis and lumbar lordosis, and the intervertebral disks were "ballooned", giving the vertebral bodies a narrowed bi-concave outline; one thoracic vertebra was grossly collapsed anteriorly.

Histological study showed that an excess of irregularly arranged trabeculae of the medullary spongiosa, and not thickening of the cortical bone, was responsible for the irregular bone structure. There was a general lack of osteoblastic and osteoclastic activity, and numerous small fractures were present, particularly in the skull, the vertebrae, and at the ends of the long bones. In the vertebrae, bony collapse with cyst-formation was frequent. There was also absence of haematopoietic marrow, and numerous Schmorl's nodes were present. Many of the bones contained areas of cartilage which were thought to be either persistent developmental foci, or areas of callus consequent on fracture and bony collapse. A severe degree of osteo-arthritis was present in the hip-joints, and was regarded as secondary to the local alterations in bony structure.

The author regards the pathogenesis of pleonosteosis as not yet elucidated. He notes a similarity of the histological changes present to certain other bone diseases, but attributes this to the limited potentialities of reaction of the skeletal tissues rather than to essential affiliations of the disease process. It is unfortunate, as the author points out, that clinical radiographs of the affected bones could not be illustrated, but this material was destroyed in the war. *H. A. Sissons.*

Treatment of Rheumatic Conditions with a Compound containing Copper and Sodium Salicylate ("Permalon"). (Über die Behandlung rheumatischer Erkrankungen mit einer Kupfer-Natrium-Salizylat-Komplexverbindung (Permalon).) HANGARTER, W., and LUBKE, A. (1952). *Dtsch. med. Wschr.*, **77**, 870. 8 refs.

In 1939 the senior author noted that Finnish copper-miners were almost free from rheumatic affections although the incidence was high in the rest of the population. The authors believe that copper exerts a beneficial effect on focal sepsis and that in combination with sodium salicylate, as in " permalon ", it gives good therapeutic results. Permalon is non-toxic, and the blood salicylate level need not exceed 20 to 24 mg. per 100 ml. for satisfactory response; the contents of one ampoule (20 ml., containing 2 g. salicylic acid and 2·5 mg. copper) are injected intravenously daily for 8 to 14 days. To obtain comparable results with oral medication with salicylates alone would require a blood salicylate level of 35 mg. per 100 ml. and there would be many side-effects. Excellent results are claimed in rheumatic fever and other conditions, and less dramatic ones in rheumatoid and infective arthritis. [Among the " rheumatic affections " treated with excellent results were two cases of erythema nodosum and five of " sciatica-lumbago " ! Clinical details are almost non-existent.] *D. Preiskel.*

Comparative Study of the Radiological Changes in the Hip in Rheumatoid Arthritis and Ankylosing Spondylitis. (Étude comparative des altérations radiologiques des hanches dans la polyarthrite chronique évolutive de l'adulte et la spondylarthrite ankylosante.) JACQUELINE, F. (1952). *J. Radiol. Electrol.*, **33**, 219. 7 figs.

The radiologic appearances of the hip joint in rheumatoid arthritis and in ankylosing spondylitis with involvement of the hip joints differ greatly. In the early stage of rheumatoid arthritis the head and acetabulum show an irregular outline and a thin zone of dense bone adjoining the articular surfaces; most of the changes are seen in the upper and inner part of the joint, which is the zone of greatest pressure. In the more advanced stages of the disease the destructive process is more pronounced; here the head may be displaced upwards while the width of the articular space is reduced.

In ankylosing spondylitis the joint space may be narrowed or normal, but there are no destructive changes. The typical changes are dense linear streaks crossing the articular space and joining the head to the acetabulum; even in advanced cases a faint outline of the little-changed joint may be seen through the streaky formation.

A. Orley.

Comparative Study of Arthrography of the Knee Joint. HAUCH, P. P. (1952). *Brit. J. Radiol.*, **25**, 120. 15 figs, 4 refs.

Visualization of the internal structure of the knee joint may be accomplished by the injection of gas or a liquid contrast medium into the joint, or by the procedure of vacuolization, in which traction and forced abduction and adduction are applied to the joint, no injection being made. In order to compare the merits of these three methods the author examined a series of 37 patients at the Westminster D.V.A. Hospital, London, Ontario, at least two, and sometimes all three techniques being used in each case.

The results definitely favoured air or oxygen injection, which produced good visualization in practically all cases. The radiological diagnosis was proved correct at operation in nine out of eleven cases of suspected meniscus injury. In addition, the cruciate ligaments, synovia, and soft-tissue loose bodies were well seen. The results of diodone arthrography were not so good, satisfactory visualization being obtained in less than half the cases examined. Of the eleven cases of meniscus injury, a definite diagnosis could be given by this method in four only. The density of the medium obscured much soft-tissue detail. Vacuolization produced good visualization in only about 10 per cent. of cases and is considered of limited value.

[The paper is well illustrated by excellent illustrations, several examples being given of the appearances of the same joint as shown by the three different methods.]

D. E. Fletcher.

Arthrography of the Shoulder. NELSON, D. H. (1952). *Brit. J. Radiol.*, **25**, 134. 12 figs, 9 refs.

The technique employed for diodone arthrography of the shoulder at St. Mary's Hospital, London, is described. The needle is introduced 1 inch (2·5 cm.) anterior to the acromio-clavicular joint until its point is embedded in the articular cartilage of the head of the humerus, and then withdrawn slightly. (It is important to use a needle with a short bevel so as to avoid simultaneous injection into joint space and soft tissues.) An injection of 8 to 10 ml. 35 per cent. diodone is then made under screen control and a film is taken with the needle *in situ* to indicate the site of capsular puncture. Three routine antero-posterior views are then taken with the humerus in internal rotation, mid-position, and external rotation.

The normal arthrogram shows four distinct features:

(1) a thin meniscus outlining the articular cartilage on the upper half of the humeral head,

(2) filling of the subcoracoid bursa,

(3) a pool of medium in the inferior joint recess,

(4) delineation of the synovial sheath of the long head of biceps.

The subacromial bursa is filled only in the presence of an effusion. Normally the injection is painless, and any acute pain usually indicates extracapsular injection. Pain frequently occurs about half an hour after the examination, however. The appearances in cases of rupture of the supraspinatus tendon are described in detail, three grades of severity being distinguished. The essential feature is the extension of medium beyond the normal confines of the joint. In the minimal tear there is a fine hair-line extension of the normal meniscus in the region of the tendon insertion. With more severe tears the medium can be seen on successive films extending progressively into the bursa and soft tissues. Arthrography was performed in a number of cases of frozen shoulder, but showed only obliteration of the inferior recess. In osteochondromatosis purely cartilaginous

joint bodies may be demonstrated. In rupture of the long head of biceps the tendon sheath, which normally fills, fails to do so, but this condition should be obvious clinically, and arthrography is unlikely to be necessary in any but exceptional cases. *D. E. Fletcher.*

Neuropathies caused by Bony Spurs in the Cervical Spine, with Special Reference to Surgical Treatment. ALLEN, K. L. (1952). *J. Neurol. Neurosurg. Psychiat.*, **15**, 20. 8 figs, 4 refs.

In this paper are reported nineteen cases of spinal cord or root compression from spurs in the cervical spine operated upon at the Johannesburg Hospital, South Africa. In all cases there was brachialgia or progressive root and cord involvement, or both, which had resisted conservative treatment. In only one case was a small amount of prolapsed disk material found, but in all there was a bony spur traversing the canal from side to side and with varying degrees of hypertrophy of the overlying posterior common ligament.

A detailed description of eight of the cases is given, together with clinical and operative findings. Patients' ages ranged from 27 to 73 years, and in only three cases was generalized osteo-arthritis present. Radiological examination showed the spurs to be double lips arising from adjacent vertebral bodies, tapering and curving towards each other and projecting $\frac{1}{8}$ in. (3 mm.) or more outside the normal vertebral-body contour. At operation the spurs were seen to form a ridge extending across the posterior aspect of the vertebral bodies from one intervertebral foramen to the other. There were usually one or more " high points " on the ridge, in most cases laterally placed but sometimes in the midline. The spurs were composed of cancellous bone enclosed in a thin shell and covered by hypertrophied posterior common ligament. The annulus fibrosus was in its normal position, and as the edges of the spurs were tightly opposed it seemed inconceivable that disk substance could have prolapsed between them. The disk material appeared to have atrophied *in situ*. Spur formation was usually present at more than one level. The spur was related to the sympathetic nerves and plexus in the vertebral arterial canal, the mixed nerve in its dural sleeve, the anterior fibres of the emerging nerve roots, and the spinal cord. The cord was often found to be kinked and displaced backwards, and sometimes to be flattened.

On the basis of the clinical picture the cases could be divided into two groups. In the first group there was root involvement only. Pain was the dominating symptom, more than one root usually being involved, so that it was difficult to identify it as originating in any particular root. Later, paraesthesiae and sensory loss of dermatome distribution appeared, and these were more valuable in locating the side of the lesion. Pain was often unilateral, but sometimes spread to the other side. Muscle-wasting corresponding to the affected roots appeared later. In most cases more than one root on the same side appeared to be involved. In the second group cord involvement dominated the picture and pain was seldom severe. The pyramidal tracts were usually nvolved first; later, weakness and wasting of root distribution in the upper limbs appeared. Sensory disturbances seem to have been inconstant and ill-defined. Diagnosis in both groups was made on clinical grounds aided by radiological examination. Myelography was required in only three of the cases, and then merely confirmed the presence of the bony spur.

Operative indications consist of definite evidence of root or cord involvement and resistance to conservative treatment. *Brodie Hughes.*

Osteitis Deformans in Gouty and Diabetic Subjects. (L'ostéose pagétique des goutteux et des diabétiques.) SERRE, H., and MIROUZE, J. (1952). *Presse méd.*, 60, 595. 12 figs, 9 refs.

This is a report on six patients, two of whom had suffered from diabetes for more than 20 years and four from gout of several years' duration, all of whom had developed Paget's disease. The diagnosis was confirmed by radiological and histological evidence. The serum acid phosphatase level in the patients with gout was slightly, though unmistakably, raised, but there was no evidence of prostatic malignant growth. It is argued that in both groups vascular changes were causative factors in the development of osteitis deformans and that the metabolic disorders of both diabetes and gout are capable of interfering with the mineral balance in the skeleton. The authors suggest that these cases throw a new light on localized forms of Paget's disease, and that gout and diabetes could be regarded as " osteotrophic diatheses ". *L. H. Worth.*

Advantages and Limitations of Ultrasonics in Medicine. SCHWAN, H. P., and CARSTENSEN, E. L. (1952). *J. Amer. med. Ass.*, **149**, 121. 5 figs, 13 refs.

The authors explain briefly the physics and some of the biophysical problems involved in the production of heat by ultrasonics in tissues and other media. As a sound wave travels through a medium a definite fraction of the energy is absorbed in the form of heat. For example, the absorption in muscle is about twice that in fat; this is a definite advantage of ultrasonic heating over electromagnetic diathermy in which the maximum heat production is in the fatty tissue.

Since ultrasound is simply a mechanical vibration its effects on biological material are necessarily of a physical nature. The effects are either thermal or non-thermal, and both may play a significant role in treatment. The non-thermal effects can produce increased permeability of membranes. This is explained by the " stirring " action of sound on the solution on both sides of the membrane, and the consequent increase in the gradient of the ion concentration near the membrane. Another non-thermal effect is the resonant oscillation of gas bubbles in liquid, which can be responsible for the destruction of cells in the tissues. High intensities of sound may produce changes of state in the medium by the formation of gaseous cavitation and the breaking up of long-chain molecules.

After comparing the characteristics and advantages of ultrasound and microwave diathermy the authors decide in favour of ultrasound on the following grounds:

ultrasound therapy has good beaming properties, efficiently transfers energy from the source to the tissue, and has good depth of penetration and selective heating effect at the interspaces. It is emphasized that care must be exercised in its use as the therapeutic indications are not yet established. *M. H. L. Desmarais.*

Present Status of Use of Ultrasonic Energy in Physical Medicine. COUNCIL ON PHYSICAL MEDICINE AND REHABILITATION OF THE A.M.A. (1952). *J. Amer. med. Ass.*, **148**, 646. 11 figs, 9 refs.

The authors of this report recall the many exaggerated claims made for the efficacy of short-wave diathermy when it was first introduced, and point out that similar claims are now being made for ultrasonic vibrations and long lists of symptoms which are alleged to be relieved by this form of treatment are being published by German workers. As the claims made were so sweeping, animal experiments were performed to ascertain the effects of ultrasonic energy on the tissues.

It was found that in the anaesthetized dog the temperature of the bone marrow and bone could be raised without damage to the superficial tissues and that rise in temperature was more effective than that obtained with diathermy. The action of ultrasonic vibrations on nerve tissue was then investigated. It was found that they could cause paralysis of muscles by blocking the action potentials of motor nerves; the paralysis was sometimes followed by partial recovery. Histologically, there was destruction of the nerve and the effect seemed to be the same as that produced by direct heating. Similar destruction could be caused in the spinal cord, where it was more marked than in the peripheral nerves. Further experiments showed that the destruction was, in fact, produced by the heating effect of the ultrasonic energy.

Experiments were then made on the growing bones of young dogs, and showed that ultrasonic energy can be very destructive to the growing bone-ends. Further experiments were made on various tumours. It was found that there was no selective action on tumour tissue, normal tissue being damaged equally severely, and it was not possible to destroy tumours completely. Experiments on normal tissues in dogs and other animals showed that all tissues in the path of ultrasonic energy can be destroyed, the degree of destruction depending on the type and density of the tissue and the presence or absence of fascial barriers. A selective destruction of hair follicles and nerve tissue could be demonstrated.

The authors conclude that ultrasonic energy is potentially dangerous and that much more work is needed before it can be generally employed. They suggest that the effects which are obtained are mainly due to heat, and that eventually it may be possible with ultrasonic energy to obtain more valuable selective heating. *William Tegner.*

Dupuytren's Contracture treated with Vitamin E. RICHARDS, H. J. (1952). *Brit. med. J.*, **1**, 1328. 8 refs.

A series of 46 cases of Dupuytren's contracture were treated; 24 had bilateral lesions. The patients were divided into three groups according to the degree of the deformity. Vitamin E was the sole form of treatment, and in no case was any improvement noted.—[*Author's summary.*]

Classification of Arthritis of the Hip. (Une classification des arthroses de la hanche.) ROBERT, P. (1952). *Rhumatologie*, **2**, 55. 10 figs.

Restoration of Movement at the Hip in Rheumatism. (La restauration des mouvements de la hanche dans le rhumatisme.) HERBERT, J. J., and PAILLOT, J. (1952). *Rhumatologie*, **2**, 72. 6 figs, 1 ref.

Assessment of Mobility in Joints. WILLIAMS, P. O. (1952). *Lancet*, **2**, 169. 2 figs.

"Rheumatism" and Skeletal Metastases. ("Rheuma" und Skelettmetastasen.) WEINTRAUB, A. (1952). *Praxis*, **41**, 311. 4 refs.

Articular Disorders in Childhood. RICHMOND, J. B., and LENDRUM, B. L. (1952). *Illinois med. J.*, **101**, 295. 3 figs, 7 refs.

Significance of Humoral Factors in the Development of Rheumatism. (Die Bedeutung humoraler Faktoren für den Verlauf des Rheumatismus.) HARTMANN, F. (1952). *Z. Rheumaforsch.*, **11**, 65. 6 figs, 21 refs.

Muscle Changes in Connection with Rheumatoid Arthritis and Osteo-Arthritis. A Roentgenological Study of the Extremital Fat. [In English.] INGLEMARK, B. E., and FRANTZELL, A. (1952). *Acta Soc. Med. upsaline.*, **57**, 83. 6 figs, 10 refs.

Progress in the Treatment of the Rheumatic Diseases. (Fortschritte in der Behandlung rheumatischer Krankheiten.) SCHULZE, E. (1952). *Dtsch. med. Wschr.*, **77**, 715. Bibl.

Treatment of Chronic Arthritis with Placental Implants. (Die Behandlung der Arthrose mit biogenen Stimulatoren (Plazentaimplantation).) PFLUGER, W. (1952). *Wien. med. Wschr.*, **102**, 561. 14 refs.

Thyroid Implantation in the Treatment of Chronic Rheumatism. (Les implants de corps thyroide dans le traitement du rhumatisme chronique.) MATRIN, E., LEPPING, C., TROUBAT, N., KEPPING, J., and CABANNE, F. (1952). *Bull. Soc. méd. Hop. Paris*, **68**, 589.

Further Experience with Thyroid Implantation in Arthritis. (Weitere Erfahrungen mit der Schilddrusencinpflanzung bei Gelenkkrankheiten.) MANDL, F., and GYRI, W. (1952). *Wien. med. Wschr.*, **102**, 550. 3 refs.

Treatment and Care of Infantile Rheumatism (Part II). (Therapie und Heilfursorge des kindlichen Rheumatismus.) STOEBER, E. (1952). *Münch. med. Wschr.*, **13**, 599. 1 fig.

Surgery of Chronic Arthritis. (Chirurgie des arthrites et des arthroses.) HERBERT, J. J. (1952). *J. int. Chir.*, **22**, 193. 7 figs.

Ultrasonics in the Spa Treatment of Rheumatism. (Ultrasons et affections rhumatismales en milieu thermal.) FORESTIER, J., CERTONCINY, A., and LEEUW, J. DE (1952). *Rev. Rhum.*, **19**, 332.

Experimental Studies of the Mode of Action of Salicylates. (Experimentelle Untersuchungen über die Wirkungsweise der Salizylsäure.) SCHUMACHER, H. (1952). *Z. Rheumaforsch.*, **11**, 105. 48 refs.

Hyaluronidase and Rheumatism. (Hyaluronidase und Rheumatismus.) HEINLEIN, H., and RATHSCHECK, R. (1952). *Arztl. Wschr.*, **7**, 385. 2 figs, 8 refs.

Study of the Antirheumatic Efficacy of "Irgapyrin". (Estudio sobre la effectividad antirreumatica del irgapyrin.) SERRA-PERALBA, A., ANGENAULT, C., and DALMASES, R. DE (1952). *Prensa med. argent.*, **39**, 399. 1 fig., 18 refs.

Two New Concepts of the Mode of Action of Salicylates in Rheumatoid States. BENNETT, K. (1952). *J. Bowman Gray Sch. Med.*, **10**, 47. 49 refs.

Glycuronic Acid in Chronic Joint Disease. (L'acido glicuronico nelle artropatie.) PALTRINIERI, M. (1952). *Minerva med., Torino*, **43**, 267. 16 refs.

Metabolism of Glycuronic Acid in Rheumatic Disease. (Zum Glukuronsäurestoffwechsel bei rheumatischen Erkrankungen.) SÜDHOF, H. (1952). *Z. Rheumaforsch.*, **11**, 88. 2 figs, 9 refs.

Involvement of the Hip Joint in Progressive Rheumatism. (L'atteinte des articulations sacro-illiaques dans le rhumatisme évolutif.) WEIL, M. P., PERROY, A., and DUTERTRE, J. (1952). *Rev. Rhum.*, **19**, 411. 4 figs, 2 refs.

Some Concepts of Rheumatic Disease. KELLGREN, J. H. (1952). *Brit. med. J.*, **1**, 1093. 3 figs.

Urethritis-Conjunctivitis-Arthritis Triad. (Aspects actuels de la triade urétrite-conjunctivite-arthrite.) DAGUET, G. (1952). *Ann. Derm. Syph., Paris*, **79**, 149. 10 figs, bibl.

Sciatica

Low Back Pain due to Anomalies of the Epidural Vessels. Pathology of the Intraspinal Venous Plexus. (Lombosciatiques par anomalies vasculaires épidurales. Contribution a l'étude de la pathologie du plexus veineux intrarachidien.) GLOOR, P., WORINGER, E., SCHNEIDER, J., and BROGLY, G. (1952). *Schweiz. med. Wschr.*, **82**, 537. Bibl.

In this paper, from the Pasteur Hospital, Colmar, the authors review 181 cases of low back pain in which they have operated since 1948. They found that in 136 cases (75 per cent.) the cause was herniation of a vertebral disk; the remaining 45 cases were due to a variety of causes, the most frequent being varicosities of the epidural vessels, which occurred in twelve (6·2 per cent.) patients. The clinical picture and myelographic appearance in these cases closely resembled those in the cases due to herniated disk, for in both lesions the radicular pain is of mechanical origin, the abnormally dilated epidural vessels acting like an extruded disk to cause pressure on the spinal roots. That this occurs most frequently at the level of L5-S1 may be explained by the anatomical fact that the spinal roots are in the closest contact with the anterior surface of the spinal canal at this level, and are thus more exposed to pressure than at other levels. Discussing the causation of the varicosity, the authors suggest that all conditions which raise the intra-abdominal or intrathoracic pressure, either acutely and repeatedly or continuously, can lead to the formation of epidural venous dilatations.

In the authors' opinion the differential diagnosis of epidural varicosity from herniated disk cannot be made before operation. In both cases the clinical picture is very similar, and the radiographs show the same notch at the point of pressure. They add the warning that a herniated disk and epidural varicosity may both be present in the same patient, as they found in a number of their cases. In a note on contrast media the authors deprecate the use of iodized oil for myelography in cases of sciatica because of the pain it may cause. It may advantageously be replaced by sodium mono-iodomethane sulphonate, as has been pointed out by Woringer and others; this substance produces no undesirable effect and gives good radiographic definition. *E. Forrai.*

***X*-ray Visualization of the Intervertebral Disk. With a Consideration of the Morbidity of Disk Puncture.** GARDNER, W. J., WISE, R. E., HUGHES, C. R., O'CONNELL, F. B., and WEIFORD, E. C. (1952). *Arch. Surg., Chicago*, **64**, 355. 4 figs, 15 refs.

The authors report their experience at the Cleveland Clinic with the technique of radiological visualization of the intervertebral disk by the direct injection of contrast medium, as described by Lindblom (*Acta orthop., scand.*, 1948, **17**, 231). They inject 0·5 to 2·0 ml. 35 per cent. diodone, and immediately after the injection lateral and antero-posterior radiographs are taken. In normal cases the injection meets with much resistance, but is usually painless, and the appearance is usually of a bilocular collection of dye occupying the middle third of the disk. With the "degenerative" type of nucleus the dye shadow is no longer discrete, but spreads in an irregular fashion throughout the entire disk and may extend beyond the margin of the vertebral bodies; the injection again meets with resistance but is painless. A similar appearance is seen in the degenerated type with posterior protrusion, but the dye is also present beneath the posterior spinal ligament, which is seen to bulge into the lumen of the spinal canal, and may be extruded into the epidural space, the column of dye thus formed showing a concave deformity produced by the protruding disk. In this type of case there is less resistance to injection, and

the patient's sciatic pain is often reproduced. In normal disks the dye is usually visible up to 12 hours after the injection, whereas in pathological conditions it disappears within a few minutes.

In a series of 89 patients, 186 injections were attempted and satisfactory radiographs obtained in 169. A high correlation between the radiological diagnosis and the findings at operation in 48 of these cases was found. One of these patients developed an abscess of the disk, from which *Staphylococcus albus* was isolated, 4 days after injection had shown a protrusion to be present. This was treated with antibiotics before operation. Of the remaining 41 patients, who were treated conservatively for periods varying from 1 to 7 months after the injection, none has returned with new or different symptoms that could be attributed to the injection.

The authors conclude that the value of this procedure in relation to myelography cannot yet be established, and point out the following disadvantages: (1) it is not free from complications; (2) much experience is needed in carrying out the injection and in interpreting the results; and (3) a tumour of the cauda equina may easily be overlooked which would have been seen on myelography.

W. B. D. Maile.

Kidney Changes in Gout. KESCHNER, H. W. (1952). *Delaware St. med. J.*, **24**, 67. 2 figs, 5 refs.

Paraesthesiae and Clinical Pharyngeal Manifestations of Gouty Rheumatism. Their Treatment with Piperazine. (Les paresthésies et manifestations pharyngées chroniques chez les rhumatisants goutteux. Leur traitement par la pipérazine.) JACOD, M. M. (1952). *Lyon méd.*, **186**, 393.

Changes Typical of Paget's Disease in Gout. (Les remaniements pagetiques de la goutte.) SERRE, H., and MIROUZE, J. (1952). *Rev. Rhum.*, **19**, 432. 6 figs, 10 refs.

Non-Articular Rheumatism

Scalenus Syndrome. [In English.] GYLLING, M. (1952). *Acta chir. scand.*, **102**, 475. 22 refs.

The author reviews the results obtained in sixteen patients followed up from 4 months to 5 years after operation for cervical rib, scalenus syndrome, and brachialgia at the Red Cross Hospital, Helsinki. Very satisfactory relief was found where before operation there had been definite evidence of compression of the lowest two roots of the brachial plexus. In cases where the initial clinical features pointed to involvement of the other roots of the plexus, or where there was radiological evidence of spondylosis of the cervical spine, the post-operative results were poor. *John Huston.*

Stenosing Tenovaginitis at the Wrist and Fingers. Report of 423 Cases in 369 Patients with 354 Operations. LAPIDUS, P. W., and FENTON, R. (1952). *Arch. Surg., Chicago*, **64**, 475. 2 figs, 4 refs.

Attention is called to frequently occurring stenosing tenovaginitis at the radial styloid and at the flexor sheath of the fingers, which are often misdiagnosed. A series of 369 patients with 423 sheaths involved and 254 operations performed, is analysed. In a great majority the condition is an occupational one and, therefore, compensable in the industrial workers.

Although spontaneous recovery may occur, operative release is preferable, particularly when symptoms are present more than one month. Operative technique is described; the importance of skin incisions along the skin creases (transverse at the radial styloid), suturing of the skin only, and immediate post-operative mobilization, is emphasized.—[*Authors' summary.*]

Non-Articular Rheumatism (Fibrositis). LAHA, P. N. (1951). *Indian med. Gaz.*, **86**, 551. 1 ref.

Tenosynovitis of the Long Head of the Biceps Brachii: a Rare Form of Scapular-Humeral Periarthritis. (La téno-synovite du long biceps forme trop peu connue de la périarthrite scapulo-humérale.) SÈZE, S. DE, and DENIS, A. (1952). *Rev. Rhum.*, **19**, 329.

Adjuvant Method of Treatment in Obstinate Fibrositic Periarthritis of the Shoulder. (Methode adjuvante de traitement dans la periarthrite fibrosante rebelle de l'epaule.) DUPOIS, P. V. (1952). *Rev. Rhum.*, **19**, 425. 3 figs, 9 refs.

General Pathology

Evidence that Aschoff Bodies of Rheumatic Myocarditis develop from Injured Myofibers. MURPHY, G. E. (1952). *J. exp. Med.*, **95**, 319. 33 refs.

The theory advanced in this paper is that myocardial Aschoff bodies evolve from focal injury to cardiac myofibres, and that certain elements in these lesions are directly derived from the muscle fibre or its ensheathing sarcolemma. The material studied was taken from twelve patients, aged from 1 to 19 years, who died during the first or second attack of rheumatic fever, and from three rabbits, 5 to 22 months old. The rabbits were examined 8 to 15 days after the last of a series of streptococcal injections (as described by Murphy and Swift in previous papers in this series (*J. exp. Med.*, 1949, **89**, 687, and 1950, **91**, 485; *Abstracts of World Medicine*, 1950, **7**, 223, and **8**, 598)). No micro-organisms were seen in sections specially stained for the purpose in any of the hearts examined, nor, in the rabbits, were *post-mortem* blood cultures positive.

By a series of 32 photomicrographs showing comparable lesions in the rabbit and human beings, the author demonstrates an apparent sequence, starting with an injured muscle fibre surrounded by basophilic and multinucleated syncytial-cell masses, " probably myogenic ", and progressing to the classical Aschoff nodule. In the rabbit material the earliest lesions appeared in the myofibrils, which became necrotic and, when stained with haematoxylin and eosin, somewhat resembled what has been called " fibrinoid necrosis ". They also became surrounded with syncytial and basophilic multinucleated cell masses originating from beneath the sarcolemma.

In some instances, in both rabbit and human, grossly necrotic areas of cardiac papillary muscle might be seen. Human skeletal muscle in one case also showed somewhat similar degenerative lesions. It is not yet clear what mechanism is responsible for this damage to the myofibrils. In the lesions illustrated there was no fibrinoid change in or between collagen fibres (as shown in previous communications), and the author considers that this is not an essential or primary change in the development of the Aschoff body.

The very close similarity between the lesions developed in a few of the rabbits subjected to repeated focal infections and the lesion in human beings supports the author's view that at least one factor in the pathogenesis of rheumatic fever is repeated infection with Group A β-haemolytic streptococci of differing serological type.

E. G. L. Bywaters.

Structure of Connective-tissue Fibres. (Строение волокнистых структур соединительной ткани.) ORLOVSKAYA, G. V., and ZAIDES, A. L. (1952). *Arkh. Patol.*, **14**, 51. 8 figs, 11 refs.

Collagen fibres of human skin, and the reticulin fibres from embryonic skin and from the fibrous framework of the spleen were studied histologically, biochemically, and by means of *X*-ray diffraction. The transformation of the embryonic reticulin fibres into collagen could be observed both histologically and by *x*-ray diffraction. It was seen that the embryonic reticulin fibres have a different structure from those of the adult. It was also established biochemically that the reticulin adsorbs less water from the air than collagen, and that it contains a greater quantity of non-combustible residue, less nitrogen, more sulphur, and more carbohydrate. The argentophilia of reticulin is probably associated with its sulphur content.

L. Crome.

Some Supravital Observations on the "L.E." Phenomenon. ROHN, R. J., and BOND, W. H. (1952). *Amer. J. Med.*, **12**, 422. 10 figs, 17 refs.

A review is given of current views on the nature of the inclusion bodies found in the polymorphonuclear neutrophils of the bone marrow and peripheral blood in many cases of acute disseminated lupus erythematosus (the "L.E." phenomenon). Five cases are described, and details are given of the method employed at Indiana University Medical Center for demonstrating the bodies by means of the supravital staining technique of Sabin. Bone-marrow preparations are more reliable than peripheral blood. By this method the bodies appear as colourless amorphous masses in which neutrophilic granules are seen, together with an autolysed nucleus which later takes on a dark orange colour. From studies of these preparations the authors confirm the finding of Lee and others (*Amer. J. Med.*, 1951, **10**, 446; *Abstracts of World Medicine*, 1951, **10**, 302) that the bodies are ingested autolysed polymorphonuclear leucocytes, individual cells having been followed throughout the process of degeneration, and their ingestion by other granulocytes observed.

Marjorie Le Vay.

Effect of Hypochromasia on the Specific Gravity and Sedimentation of Red Cells. ROGERS, K. B. (1952). *Brit. med. J.*, **1**, 1109. 17 refs.

The author briefly discusses from the theoretical aspect the effect of a change in the specific gravity of the erythrocytes on their sedimentation rate. He points out that owing to the high molecular weight of haemoglobin in relation to that of the proteins of the cell stroma, a reduction in haemoglobin content should result in a reduction in the specific gravity of the erythrocyte and in its rate of fall.

In 37 specimens of blood he found that the specific gravity of the packed erythrocytes bore a direct relationship to the mean corpuscular haemoglobin content (M.C.H.C.), cells with a low M.C.H.C. having a low specific gravity. By separating the erythrocytes and plasma of blood from two patients with hypochromic anaemia and a low erythrocyte sedimentation rate (E.S.R.) and mixing them in various combinations with erythrocytes and plasma from normochromic blood with a high E.S.R. he showed that erythrocytes with a low specific gravity (that is, hypochromic) sediment more slowly than normochromic erythrocytes when suspended in the same plasma. It is suggested that the finding of a low E.S.R. in certain cases of severe hypochromic anaemia (Terry, *Brit. med. J.*, 1950, **2**, 1926; *Abstracts of World Medicine*, 1951, **9**, 598) does not necessarily prove that the E.S.R. is unaffected by the presence or absence of anaemia, but may be merely an indication that in these cases the reduction in specific gravity of the hypochromic erythrocytes is sufficient to neutralize the sedimentation-accelerating effect of a reduced cell concentration.

R. F. Jennison.

Histopathology of Muscle in Rheumatoid Arthritis and Other Diseases. TRAUT, E. F., and CAMPIONE, K. M. (1952). *Arch. intern. Med.*, **89**, 724. 10 figs, 15 refs.

The authors, after reviewing the relevant literature, describe their histological findings in sections of the gastrocnemius muscle of sixteen patients with rheumatoid arthritis, aged 41 to 80 years; three of these cases were complicated with amyloidosis, and one with amyotrophic lateral sclerosis. All except one had erythrocyte sedimentation rates above 18 mm./hr. Similar muscle specimens were obtained as controls from ten patients with muscle wasting, suffering from such diseases as Parkinsonism, hemiplegia, pulmonary tuberculosis, and cancer. Sections were also studied from the muscles of rabbits immobilized in plaster casts, and from several patients with various diseases of the connective tissue such as disseminated lupus erythematosus, dermatomyositis with arthritis, gout, serum sickness, and rheumatic fever (six patients). Two blocks were taken from each patient, one fixed in formalin and the other in Zenker's solution, and between six and ten sections were cut at varying levels from each block.

The rheumatoid patients showed muscle atrophy, with fat infiltration and some focal degeneration and scarring. There was an increase in the number of interfibrillar nuclei which was more than could be accounted for by atrophy. These nuclei also appeared to be larger and paler than normal nuclei, and occasionally were grouped

to form definite cells of Sternberg type. There were perivascular infiltrations in fifteen of the sixteen patients with rheumatoid arthritis; no change was seen in one patient after treatment with cortisone for 2 weeks. In conditions other than rheumatoid arthritis a similar atrophy and nuclear increase was seen. In both rheumatoid arthritis and in disuse atrophy there were focal interfibrillary collections of round cells. The authors conclude that " perivascular infiltration was the only unusual finding peculiar to rheumatoid arthritis in muscles of many conditions studied ". *E. G. L. Bywaters.*

Cell Membrane Defect in Acute Rheumatic Fever. AIKAWA, J. K. (1952). *N.C. med. J.*, **13**, 330. 5 refs.

ACTH, Cortisone, and Other Steroids

Assessment of rapidly acting Agents in Rheumatoid Arthritis. Observations on Deoxycortone with Ascorbic Acid, ACTH, and Cortisone. LOXTON, G. E., LE VAY, D., and STANFORD, B. (1952). *Lancet*, **1**, 1280. 4 figs, 30 refs.

For assessing rapid changes in the rheumatoid state, purely objective measurements of the state of the joints are unsatisfactory, as they are relatively insensitive, do not confirm clinical observations, and take no account of subjective changes. On the other hand, purely subjective factors cannot be measured precisely enough for test purposes. The authors therefore recommend that such assessments be based on objectively measurable factors which are affected by subjective changes, that is, certain components of joint function such as range and speed of movement, dexterity, and strength of grip. These factors must be such that accurate measurement can be made, and that some reasonable, even if arbitrary, standard of normality can be fixed. The function to be measured must also be impaired and capable of improvement, while skilled functions must be avoided in which normal standards change with practice. Joint-goniometry and grip-dynamometry are too inaccurate and insensitive to be of use in the measurement of functional changes. With these considerations in mind the authors have devised a technique for assessing the effect, in cases of rheumatoid arthritis, of certain rapidly acting drugs on the range of active joint movement and on joint " mobility " (that is, speed of movement). For this purpose an ingenious device is used whereby still and ciné photographs are taken as the patient performs certain movements, the range and speed of which can then be accurately measured. The results are expressed as percentages of arbitrary normal values derived from examination of the active range of mobility of a series of normal joints by the same technique.

In a series of measurements on 31 patients (seventy joints) a statistically significant degree of improvement followed within an hour of the injection of 5 mg. deoxycortone and 1 g. ascorbic acid in 21 cases, but no significant change followed saline injections. The improvement was not usually maintained for longer than a week. In three out of four patients who were given 25 mg. corticotrophin intravenously, a well-marked improvement was observed within 1 hour, and up to 12 hours.

The authors consider that their findings confirm the original observations of Lewin and Wassén (*Lancet*, 1949, **2**, 993; *Abstracts of World Medicine*, 1950, **7**, 522) of the beneficial effects of deoxycortone and ascorbic acid in rheumatoid arthritis. To account for the conflict that has arisen over the merits of this therapy the authors stress the importance of time-relation between the injection and its effect—the average duration of the response is about 8 hours and may be only 30 minutes. In addition, the response is inconstant, varies in magnitude, and may be followed by exacerbation. Reasons are given for believing that deoxycortone and ascorbic acid act in essentially the same way as does cortisone, but in an accelerated manner. *Ellis Dresner.*

Changes in Carbohydrate Metabolism during Treatment with Cortisone and their Explanation. (Étude et essai d'interprétation de certains troubles du métabolisme glucidique observés au cours du traitement par la cortisone.) COSTE, F., BONFILS, S., DELBARRE, F., and CIVATTE, J. (1951). *Pr. méd.*, **59**, 1565. 12 refs.

The authors have studied glucose metabolism in patients receiving cortisone for the treatment of arthritis at the Rheumatological Clinic of the Paris Faculty of Medicine. Blood samples were taken for estimation of sugar and pyruvate content at 30-minute intervals following the administration of 50 g. glucose to the fasting patient before and during treatment with cortisone in nineteen cases, in six of which the patient received the cortisone together with cocarboxylase. In those receiving cortisone alone there was no constant change in the blood sugar curve, but a fairly marked general rise was seen in the blood pyruvate level after a total dose of 1 to 2 g. had been given. The addition of cocarboxylase to cortisone therapy in a dose of 2 to 3 g. a day prevents this rise in blood pyruvate level. The authors suggest that cortisone may inhibit the breakdown of pyruvate and that this may be a factor in its antirheumatic action. *G. S. Crockett.*

Effect of Cortisone on Blood Clotting. Observations in One Case of Haemophilic Arthritis and Four Cases of Rheumatoid Arthritis. (Efeito do cortisone sôbre a coagulação sanguinea. Observação sôbre uno caso de artrite hemofílica e quatro de artrite reumatóide.) SENISE, N. (1952). *Med. Cirurg. Farm.*, **190-191**, 96. 12 figs, 6 refs.

The author presents one case of haemophilic arthritis and four cases of rheumatoid arthritis treated with cortisone, in which variations in clotting time were observed. A remarkable shortening of clotting time was caused by the hormone and this was particularly noticed in the case of haemophilic arthritis.

The hypercoagulation of the blood resulting from cortisone therapy, draws attention to the possibility of accidents if it is administered without special care to prevent thrombo-embolic phenomena. [*Author's summary.*]

Relation between the Effects of Corticotrophin on the Blood and Bone Marrow, with Special Reference to the Eosinophil Cells. (Über die Beziehungen zwischen Blut- und Knochenmarkswirkungen des adrenocorticotropen Hormons, besonders bei den Eosinophilen.) GROSS, R., and SIECKE, U. (1952). *Klin. Wschr.*, **30**, 456. 2 figs, 36 refs.

The effect on the blood and bone marrow of a single injection of 50 mg. of corticotrophin was investigated in eight normal males, while one case of chronic polyarthritis treated with 1,200 mg. of corticotrophin, was similarly examined.

The fall of eosinophil leucocytes in the peripheral blood was not accompanied by a decrease of these cells in the marrow: indeed, here there was a slow increase, especially of young forms, during a course of treatment. The authors suggest that the following several factors may play a part in producing this phenomenon: destruction of cells in the peripheral blood; redistribution of the cells in the circulation; and inhibition of maturation and of emigration from the formative tissue. *A. Piney.*

Effect of ACTH on the Erythrocyte Sedimentation Rate and Plasma Fibrinogen and Serum Protein Levels in Normal Persons. FEARNLEY, G. R., and BUNIM, J. J. (1951). *Lancet*, **2**, 1113. 3 figs, 14 refs.

Elevation of the plasma fibrinogen level has been shown to be the most important factor causing a high erythrocyte sedimentation rate (E.S.R.) in acute disease, and it has previously been shown that under ACTH therapy the fall in the E.S.R. is paralleled by a fall in the plasma fibrinogen level.

In a preliminary experiment the authors have demonstrated the rapidity of the "rebound" to high levels when ACTH is discontinued. They describe the effect of injection (usually of 40 mg.) of ACTH on the plasma fibrinogen level and the E.S.R. of seven healthy subjects. Haematocrit values and serum protein levels were also studied, but showed no consistent or significant change. In four of the subjects (in one of whom the experiment was repeated four times) the plasma fibrinogen level fell after injection; the extent of the fall varied even in the same subject. In two subjects the plasma fibrinogen level rose after injection, and in one there was no significant change. In only one test was there a fall in E.S.R. of any magnitude; this was accompanied by the greatest observed fall in level of plasma fibrinogen (from 300 to 245 mg. per 100 ml.). Haematocrit values suggested that changes in blood volume during the tests were of the order of 2 to 5 per cent. In two subjects injections of saline were given as a control. Only very small alterations in plasma fibrinogen level were observed; these could be explained by the haematocrit changes.

The authors comment that the plasma fibrinogen level, and similarly the E.S.R., will tend to be raised by an inflammatory process and lowered by the administration of ACTH or cortisone. The actual levels will be a resultant of these two effects. The action of cortisone or ACTH appears to be non-specific, and it may be that with these drugs active inflammation may continue, masked and with a normal E.S.R. It is prudent, therefore, to regard the E.S.R. as an unreliable index of rheumatic activity in patients under the influence of ACTH and cortisone. *B. E. W. Mace.*

Effects of ACTH and of Cortisone on the Platelets in Idiopathic Thrombopenic Purpura. JACOBSON, B. M., and SOHIER, W. D. (1952). *New Engl. J. Med.*, **246**, 247. 3 figs, 6 refs.

The authors describe the treatment with corticotrophin (ACTH) and cortisone of three patients with idiopathic thrombocytopenic purpura at the Massachusetts General Hospital and its effects on the platelet count. In each case, on giving ACTH parenterally and cortisone by mouth, a rise of the platelet count to high levels was observed, beginning between the second and fourth days of treatment. The count rapidly fell 7 days after the last dose. In two cases splenectomy had previously been performed, but this did not prevent the rise in platelet count. In the third case splenectomy was performed after cortisone had been given, and was followed by a rise in platelet count. The authors quote one case of severe thrombocytopenia associated with cirrhosis of the liver in which treatment with cortisone and ACTH did not affect the platelet count. They suggest that ACTH or cortisone may be of use in preparing for splenectomy or in tiding over a critical bleeding episode.

[In an addendum, reference is made to a paper by Bethel and others (*Proceedings of the Second Clinical ACTH Conference, Philadelphia*, 1951) describing remissions of several months' duration in cases of thrombopenic purpura after similar treatment.] *T. M. Pollock.*

Effect of Corticotropin (ACTH) on Myelomatosis with Special Reference to the Bone Marrow and the Serum Proteins. [In English.] EFFERØSE, P., GORMSEN, H., HARBOE, N., NIELSEN, S. E., and VIDEBAEK, A. (1952). *Acta med. scand.*, **143**, 63. 7 figs, 33 refs.

Corticotrophin prepared from pigs' pituitaries was given to six patients with multiple myelomatosis in courses of 10 units five times daily for 12 days. One of the patients had been treated with urethane just before, and another had a course of corticotrophin 1 year previously. The patients developed nausea and diarrhoea. Bone pain disappeared in all, but moderate oedema developed. Changes in body weight were not constant. During the course of treatment the excretion of neutral 17-ketosteroids rose and the eosinophils largely disappeared from the peripheral blood. Though the urea clearance did not change, the blood urea level often rose. In two patients the erythrocyte sedimentation rate fell markedly during treatment; in four the excretion of protein in the urine increased, though the excretion of Bence Jones protein decreased with treatment. The serum globulin level in the blood decreased during treatment and rose again afterwards. The composition of the bone marrow was repeatedly estimated by sternal punctures, in smears and in histological preparations, but no changes were found either quantitatively or morphologically that could be attributed to the treatment with corticotrophin. *E. Neumark.*

Effect of Repeated Injections of ACTH upon the Bone Marrow. HUDSON, G., HERDAN, G., and YOFFEY, J. M. (1952). *Brit. med. J.*, **1**, 999. 10 refs.

The effect of repeated injections of corticotrophin on the bone marrow of guinea-pigs of the Mill Hill strain, 4 to 6 months old, was studied. In seven normal guinea-pigs blood from an ear vein was taken for a blood count, the guinea-pigs then being killed and the bone marrow examined. To nine other guinea-pigs, after a blood count, daily intraperitoneal injections of 1 mg. corticotrophin were given for 7 days. The corticotrophin was dissolved in 0·3 ml. physiological saline containing 0·001/N HCl. At the end of the course of injections another blood count was made, the animals were killed, and the marrow was examined.

Absolute and differential blood counts were made with Wright's stain and water at *p*H 6. The eosinophils were counted by a modification of Randolph's technique, a mixture of equal parts of propylene glycol and 0·05 per cent. phloxine in water being used as the diluent. Reticulocytes were counted by the brilliant cresyl-blue method—1 per cent. in absolute alcohol allowed to dry on the slide. Marrow from the humerus was ejected into a known weight of human plasma in a tube and the weight of marrow obtained by difference. The tube was shaken 400 times per minute for 3 minutes in a mechanical shaker to suspend the cells. Marrow smears and eosinophils were stained by the methods indicated above.

The marrow as a whole appeared to show increased cellularity in the corticotrophin-treated animals and there was an increase in the number of myeloid cells. There were no significant changes in the marrow lymphocytes. The relationship of corticotrophin to the bone marrow is discussed. *Norval Taylor.*

Resistance to Corticotropin, Cortisone, and Folic Acid Antagonists in Leukemia. PILLERS, E. M. K., BURCHENAL, J. H., ELIEL, L. P., and PEARSON, O. H. (1952). *J. Amer. med. Ass.*, **148**, 987. 4 figs, 12 refs.

At the Sloan-Kettering Institute, Memorial Cancer Center, New York, sixteen children (Series A) were treated with corticotrophin (50 to 100 mg. per day) or cortisone (100 to 400 mg. per day) after cessation of response to anti-folic acid therapy, and six children (Series B) were treated with anti-folic acid antagonists (mainly " Amethopterin ") after they had ceased to show response to corticotrophin or cortisone. In Series A, ten patients showed a good clinical and haematological response. In Series B a good response was obtained in three patients. The authors suggest that their results point to the fact that the hormones and folic-acid antagonists have a different primary effect on the leukaemic processes, and that remissions can be induced in about 50 per cent. of patients by alternate therapy.

R. Winston Evans.

Diuretic Response to Ingested Water in Addison's Disease and Panhypopituitarism and the Effect of Cortisone thereon. GARROD, O., and BURSTON, R. A. (1952). *Clin. Sci.*, **11**, 113. 5 figs, 42 refs.

In five patients with Addison's disease and four with panhypopituitarism, studied at the Postgraduate Medical School of London, the diuretic response to a standard water load was observed during control periods, after cortisone given by injection (in all nine cases), and also orally (one case), and after injection of corticotrophin (two cases). Measurements were made of the plasma specific gravity (P.S.G.), plasma sodium and chloride levels, haematocrit (P.C.V.), thiocyanate absorption rate, renal plasma flow (R.P.F.), glomerular filtration rate (G.F.R.), and urinary sodium output. The characteristic delay in diuresis observed during control periods was not corrected by treatment with deoxycortone acetate (DCA) in the cases of Addison's disease, or DCA, testosterone, and thyroid extract in the cases of panhypopituitarism. Adequate dosage of cortisone (100 mg. daily by injection, begun 36 to 62 hours before the test, was found satisfactory) caused diuresis to start earlier, to reach higher rates of flow, and to end sooner. A similar response was observed in one patient given 50 mg. cortisone orally. In a patient with mild adrenal failure the full cortisone effect was not obtained until salt and water depletion had been corrected with DCA. One patient with impaired neurohypophyseal function developed diabetes insipidus lasting for 36 hours after an injection of cortisone, thus suggesting that adrenocortical hormone is essential for the perpetuation of diabetes insipidus.

Changes in tubular reabsorption of water during diuresis were greater after cortisone than in the control periods. The rate of output of sodium and chloride was not significantly altered by cortisone, nor was the rate of water absorption from the gut (deduced from thiocyanate-absorption rates) greatly increased. Changes in the P.C.V., P.S.G., and plasma sodium and chloride levels 2 hours after ingestion of water showed so much individual variation that no conclusions could be drawn. In one patient with hypopituitarism given corticotrophin the diuretic response was variable; in the other, consistently good. The response may be obscured by contamination of the corticotrophin with antidiuretic hormone.

It is concluded that in these patients there exists a defect in water diuresis directly related to adrenal failure, and requiring for its repair (1) correction of salt and water depletion, and (2) a specific cortisone effect. It is suggested that the latter may be by direct action on the renal tubules, allowing the inhibition of water reabsorption relative to that of solutes, in response to the stimulus of plasma hypotonicity. *H. McC. Giles.*

Role of the Pituitary and Adrenal Glands in the Inhibition of Hyaluronidase by Salicylates *in vivo*. PELLOJA, M. (1952). *Lancet*, **1**, 233. Bibl.

The author, working at the Laboratory of General Physiology, Modena, Italy, has previously presented evidence to show that the inhibition of hyaluronidase by salicylates *in vivo* is mediated by the pituitary-adrenal system. Corticotrophin and cortisone are known to inhibit the spreading action of hyaluronidase, and there is much evidence to show that salicylates and cortisone produce very similar effects.

The experiments on rats here described showed that salicylates inhibit the spreading of indian ink in the

dermis by hyaluronidase. In rats previously adrenalectomized or hypophysectomized this inhibition did not take place. *G. S. Crockett.*

Hypopituitarism with Pituitary Tumours. Cortisone in the Treatment of Stupor associated with Hypopituitarism. CAUGHEY, J. E., JAMES, A., and MACLEOD, E. K. (1952). *Brit. med. J.*, **1**, 1216. 11 refs.

In three cases of chromophobe adenoma of the pituitary gland and one of craniopharyngioma, the tumour was removed at operation. In all the patients there were clinical signs of hypopituitarism which was confirmed by insulin sensitivity tests and estimation of the urinary excretion of 17-ketosteroids. Immediately after operation the patients passed into a semicomatose state in which the pulse could be felt, the superficial and deep reflexes were present, but there was marked confusion, disorientation, and incontinence. Amnesia continued for the period of stupor. One of the four patients gradually recovered within 6 weeks without treatment. Another patient, after having been semicomatose for 2 weeks, received an implant of 200 mg. testosterone and 100 mg. deoxycortone acetate, together with daily doses of sodium chloride and thyroid; he started to improve markedly 6 days later and made a good recovery. The two remaining patients, who were given 200 mg. cortisone daily when the stupor started, responded after 28 and 48 hours respectively; cortisone was later replaced by testosterone, deoxycortone acetate, and thyroid.

H. Herxheimer.

ACTH in Hypopituitarism. ROLLAND, C. F., and MATTHEWS, J. D. (1952). *Brit. med. J.*, **1**, 1220. 2 figs, 7 refs.

The authors describe three cases of hypopituitarism in which the basal metabolic rate was low and the excretion of 17-ketosteroids was reduced; three further cases are mentioned briefly in an addendum. The patients received 50 to 75 mg. corticotrophin daily over a period of 10 days. A marked subjective improvement became apparent on the third day of treatment and persisted until about 3 days after treatment stopped, when a relapse began. Testosterone and thyroid were then substituted [but the effect of this treatment is not reported]. The subjective improvement was accompanied by objective signs of improvement—a decrease in insulin sensitivity and an increase in capillary resistance in one patient and an increase in urinary excretion of 17-ketosteroids or of corticoids in the other two patients.

H. Herxheimer.

Some Effects of Cortisone on Metabolic Disturbance Associated with Renal Edema. KEITH, N. M., POWER, M. H., DAUGHERTY, G. W., and KEITH, H. M. (1952). *Arch. intern. Med.*, **89**, 689. 9 figs, 47 refs.

Metabolism was studied in three patients suffering from renal oedema of the nephrotic type who were receiving cortisone. There was an increase in catabolism accompanied by an increase in oedema during the early stages of treatment; this was followed by a diuresis and loss of oedema in two patients. In one patient proteinuria disappeared. *G. M. Bull.*

Lipoid Nephrosis and its Treatment with ACTH (Corticotrophin). (La nefrosi lipoidea ed il suo trattamento con ormone corticotropo (A.C.T.H.).) TANGHERONI, V., and BOTTONE, E. (1952). *Riv. Clin. pediat.*, **50**, 345. 3 figs, 28 refs.

The authors review modern ideas on the aetiology and mechanism of nephrosis and the part played by endocrine glands in this disease, and summarize the favourable reports on corticotrophin therapy in recent American literature. They then describe the case of a 5-year-old child who developed a fever and cough, followed in a few days by oedema, oliguria, and albuminuria. On admission to hospital he presented the classical picture of nephrosis, with generalized oedema, gross albuminuria, low plasma protein and high lipid contents, and a hypochromic anaemia. He was treated during the first month with penicillin and thyroid, but his condition steadily deteriorated and it was decided to try the effect of corticotrophin. He was given 36 mg. daily for 3 days, followed by 48 mg. daily for a further 8 days, after which the drug was stopped abruptly.

Though there was some improvement in well-being during treatment, there was only a slight increase in urinary output, and some reduction in the oedema and albuminuria after stopping the drug. Extensive investigations were carried out during the period of observation, but apart from demonstrating the metabolic activity of corticotrophin they failed to show any significant effect on the nephrotic picture itself. The patient continued to deteriorate and abdominal paracentesis became necessary. After a further month corticotrophin (48 mg. daily for 10 days) was again given, but the response was negligible; soon afterwards the patient was discharged at the request of the parents. The authors concluded that the value of corticotrophin in the treatment of nephrosis is as yet unproven.

[For details of the biochemical findings the original paper should be consulted.] *A. Paton.*

Cortisone in Asthma. MITCHELL, H. S., and CAMERON, G. (1952). *Canad. med. Ass. J.*, **66**, 313. 7 refs.

Cortisone and cortisone with corticotrophin were given to 21 patients, four females and seventeen males, suffering from severe intractable asthma. The cortisone was given intramuscularly or orally in doses of 200 to 300 mg. for 2 days, followed by 100 mg., reducing to 50 mg. daily. There was marked improvement in nine patients, slight improvement in five, and no improvement in seven. Of the nine patients showing marked improvement, four obtained complete subjective and objective relief of symptoms, two of these having been given corticotrophin for the first 2 days with cortisone. Most of the patients who did not respond had severe emphysema and chronic bronchitis of long standing. The response was observed in 24 hours to 6 days after the treatment started, the maximum benefit being obtained within 3 to 9 days, except in two cases, when the maximum benefit was observed as late as the 12th and 17th days respectively. Relapses occurred 1 week to 3 months after treatment was stopped. Three patients with status asthmaticus responded dramatically to cortisone. *J. Pepys.*

Adrenocorticotropic Hormone (ACTH) and Cortisone: their Effect on Intradermal Reactions. [In English.] ANDERSON, E. (1952). *Acta allerg., Kbh.*, **5**, 58. 5 figs, 14 refs.

Corticotrophin and cortisone may be used with dramatic though generally temporary benefit in cases of asthma, yet there is no effect on the type of skin reaction or reaction to histamine. However, in two cortisone-treated patients sensitive to dust there was a reduction in size of the weal when they were pre-treated with 0·5 ml. adrenaline subcutaneously. *A. W. Frankland.*

Treatment of Exfoliative Dermatitis with Cortisone. WEST, B. M. (1952). *Arch. Derm. Syph., Chicago*, **65**, 56. 11 refs.

The intramuscular administration of cortisone effected a rapid cure of generalized dermatitis in three patients in a U.S. Veterans Administration Hospital, each of whom gave a history of psychosis. The dermatitis had resulted as a reaction to various local applications used in the treatment of eczema. *John T. Ingram.*

Effect of Testosterone on Patients with Bone Metastases. LASZLO, D., SCHILLING, A., BELLIN, J., GOTTESMAN, E. D., and SCHULMAN, C. A. (1952). *J. Amer. med. Ass.*, **148**, 1502. 5 figs.

In this report to the Council on Pharmacy and Chemistry of the American Medical Association the effect of testosterone on the mineral metabolism of six patients with osteolytic metastases secondary to carcinoma of the breast is described. In three of the cases more rapid osteolysis and hypercalcaemia were induced, and in no case was benefit derived from the treatment.

Comparison was made between these cases and others with bone metastases arising from different types of malignancy. A patient with osteolytic metastases secondary to leiomyosarcoma of the vulva was given testosterone; urinary nitrogen excretion fell immediately and calcium loss was slightly less, but there was no major improvement in calcium metabolism. In a case of multiple myeloma with extensive osteolysis, 15 mg. stilboestrol was given daily for 54 days with some improvement in calcium balance; later, 50 mg. testosterone per day was given for 60 days and this resulted in a decreased urinary nitrogen excretion with slight improvement in mineral balance. In a premenopausal patient with osteolytic metastases secondary to breast carcinoma, radiation castration induced a temporary improvement in mineral and protein balance. Five cases are described in detail with graphs showing the metabolic data. *H. G. Crabtree.*

Response of Otosclerosis and Adhesive Otitis to Treatment with Corticotropin. RISKAER, N. (1952). *Arch. Otolaryng., Chicago*, **55**, 343. 1 fig., 7 refs.

At Sundby Hospital, Copenhagen, corticotrophin was tried in the treatment of two cases of adhesive otitis following fenestration, 20 to 30 mg. being given intramuscularly four times daily for 8 days, with no result. In a third case deafness due to otosclerosis had been present for many years in the right ear, and there had been progressive impairment of hearing in the left ear for 3 months. There was no immediate improvement on either side when corticotrophin was given, so fenestration was performed on the right side. During the next 6 weeks hearing improved in both ears, especially on the unoperated side, and the author attributes this improvement to corticotrophin. In nine cases of closed fenestra or loss of post-operative improvement for other reasons following fenestration for otosclerosis 9 to 30 months previously, the hearing was not affected by treatment with corticotrophin. Treatment with corticotrophin immediately following fenestration, however, is said to have given good primary results in two further cases, but in these the observation period after operation has not exceeded 3 months. Apart from considerable fluid retention the patients do not seem to have suffered in any way from the treatment.

The theoretical basis of this treatment is that corticotrophin, having an inhibitory effect on mesenchymal activity, might be expected to diminish the liability to formation of bone or fibrous tissue in or around the fenestra. *F. W. Watkyn-Thomas.*

Treatment of Ulcerative Colitis with Corticotrophin (ACTH) and Cortisone. GRAY, S. J., REIFENSTEIN, R. W., BENSON, J. A., and YOUNG, J. C. G. (1952). *J. Amer. med. Ass.*, **148**, 1489. 4 figs, 9 refs.

The authors report from Boston some favourable results of ulcerative colitis which had proved intractable to prolonged and extensive medical treatment. Patients were maintained on a moderately unrestricted bland diet, and all other medication, except for the use of phenobarbitone, was discontinued. Some patients receiving corticotrophin were given penicillin injections during withdrawal of the drug. Salt and fluid intake were restricted and potassium intake was augmented. Psychological factors were excluded by the use of placebos. Treatment was controlled by a large range of laboratory tests. The rationale for this form of treatment, together with the complications of the treatment and its withdrawal, are discussed. Criteria for remission were: control of diarrhoea, decrease in faecal blood, fall in lysozyme titre (which is claimed to parallel the course of the disease), disappearance of fever, decrease in erythrocyte sedimentation rate, increase in body weight, and sigmoidoscopic evidence of healing.

The initial symptomatic response was considered excellent in three, good in two, and fair in two; in the other case there was no response. None of the patients was cured, and no signs of healing were observed on sigmoidoscopic examination until after 3 weeks of treatment, when there were less bleeding and ulceration and diminished granularity. In one case with multiple strictures, polyposis, and fistulae there was no improvement and bleeding continued. A normal radiographical appearance was never achieved, though there was improvement in three cases.

Treatment varied in regard to both size of dose and duration, but the best long-term results were obtained after a prolonged course. Of the seven cases which responded to treatment, remission lasting from 10 to 28 months was obtained in four, but in the others relapse occurred from 2 to 9 months after stopping treatment.

The treatment was found useful as a preparation for surgery [though the authors do not discuss this aspect further].

ACTH was given in doses of 20 to 40 mg. intramuscularly every 6 hours for 3 to 8 weeks, with gradual reduction of dosage over the last 5 to 7 days. Later it was given intravenously, 20 mg. in 500 ml. dextrose over an 8-hour period daily. Cortisone was given orally in one or more courses of 100 to 125 mg. twice daily for 10 to 21 days, again with gradual reduction in dosage. The longest course was 133 days. *J. David DeJong.*

Effect of Cortisone on Non-tropical Sprue (Idiopathic Steatorrhea). TAYLOR, A. B., WOLLAEGER, E. E., COMFORT, M. W., and POWER, M. H. (1952). *Gastroenterology*, **20**, 203. 7 figs, 19 refs.

The effect of cortisone in the treatment of idiopathic steatorrhoea (non-tropical sprue) has been investigated clinically in six cases, with, in addition, metabolic balance studies in three of them. The cortisone was given in daily doses of 25 to 100 mg., either orally or intramuscularly, the effect being more rapid with oral administration. In all cases there were marked subjective improvement and a decrease in the number and consistency of the stools. Improvement in absorption is claimed on the basis of changes in the amount of water, solids, nitrogen, and fat in the faeces, although normal levels were not reached, the patients being still unable to tolerate an increased amount of fat in the diet and the flattened glucose-absorption curves remaining unaltered. The prothrombin time improved, but deteriorated again when the amount of fat in the diet was increased. Doses of cortisone greater than 100 mg. a day caused hypertension and oedema.

The authors claim that cortisone is of value in the treatment of exacerbations of diarrhoea in these cases, but does not seem to affect the underlying metabolic fault in idiopathic steatorrhoea. *A. C. Frazer.*

Preliminary Observations on Mental Disturbances occurring in Patients under Therapy with Cortisone and ACTH. CLARK, L. D., BAUER, W., and COBB, S. (1952). *New Engl. J. Med.*, **246**, 205. 11 figs, 35 refs.

This paper records detailed clinical and laboratory observations in ten cases in which mental disturbances occurred during treatment with ACTH (corticotrophin) or cortisone at the Massachusetts General Hospital, Boston. Although no definite relation to dosage was apparent, most of the major psychotic episodes occurred after ACTH had been given for 2½ months or more; in some cases it was noted that the onset of mental disturbance coincided with the maximum body weight recorded. The nature of the disorders varied widely.

None of these ten patients had any previous history of major mental illness, although minor abnormalities of personality had been noted in four. No characteristic of personality could be found that might have been of help in anticipating psychiatric complications.

The authors consider that if such complications occur, the dose of the drug should be reduced and a close psychiatric watch maintained; if further deterioration occurs, the drug should be entirely withdrawn. If this is done they consider the prognosis to be good, as all their patients recovered completely. *B. E. W. Mace.*

Cortisone in Alcaptonuric Osteo-Arthritis. (Il cortisone nell'osteoartrosi alcaptonurica.) D'ANELLI, A. (1952). *Policlinico. Sez. prat.*, **59**, 834. 4 refs.

Failure of Pregnenolone to maintain Remission of Rheumatoid Arthritis following Cortisone Therapy. (Ineficacia de la pregnenolona en el mantenimento de la remission lograda con cortisona en la artritis reumatoidea.) SCHAPOSNIK, F., and GUTIÉRREZ, A. (1952). *Pren. méd. argent.*, **39**, 1049. 3 figs.

Mode of Action of Cortisone and Corticotrophin in Rheumatic Disease. (Mode d'action de la cortisone et de la corticostimuline hypophysaire dans les affections rhumatismales.) COSTE, F., PIGUET, B., DELBARRE, F., and BOUREL, M. (1952). *Sem. Hóp. Paris*, **28**, 1761.

Rheumatoid (?) Plantar Perifascitis and its Response to Cortisone Therapy. KESTLER, O. C. (1952). *N.Y. St. J. Med.*, **52**, 1313. 2 figs.

Practical Considerations in the Treatment of Rheumatoid Arthritis with Cortisone and ACTH. COHEN, A., ROSE, I., and POCOCK, D. (1952). *J. Philad. gen. Hosp.*, **3**, 32. 3 refs.

Effect of ACTH on Body Water Compartment in Juvenile Rheumatoid Arthritis. [In English.] FRIIS-HANSEN, B., TUDVAD, F., and VESTERDAL, J. (1952). *Scand. J. clin. Lab. Invest.*, **4**, 36. 1 fig., 20 refs.

First Experiments in treating Rheumatic Carditis with ACTH and Cortisone. (Premiers essais de traitement des cardites rhumatismales par ACTH et cortisone.) RAVAULT, P. P., FRAISSE, H., CHASSAGNON, C., TRAEGER, J., and TANTOT, —. (1952). *J. Méd. Lyon*, **33**, 275. 20 refs.

Development of Rheumatic Aortic Endocarditis during and in spite of Intensive and Prolonged Treatment with ACTH. (Constitution d'une endocardite aortique rhumatismale au cours et en dépit d'un traitement par l'ACTH intensif et prolongé.) POST, M., TRAEGER, J., and ANNINO, R. (1952). *Lyon méd.*, **186**, 129.

Reversibility of Certain Rheumatic and Non-rheumatic Conditions by the Use of Cortisone or of the Pituitary Adrenocorticotropic Hormone. HENCH, P. S. (1952). *Ann. intern. Med.*, **36**, 1. Bibl.

Therapeutic Ineffectiveness of Cortisone in Chronic Infective Processes of the Joints. (Ineficacia terapeutica de la cortisona en procesos articulares infeccisos cronicos.) BERTANI, D. C. (1952). *Rev. argent. Reum.*, **17**, 53. 24 refs.

Continuous Intravenous Administration of ACTH. [In English.] COHEN, A. M., and EHRENFELD, E. N. (1952). *Acta endocr., Kbh.*, **10**, 128. 8 refs.

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Secretion of a Salt-retaining Hormone by the Mammalian Adrenal Cortex. SIMPSON, S. A., TAIT, J. F., and BUSH, I. E. (1952). *Lancet*, **2**, 226. 8 refs.

ACTH and Cortisone. (ACTH og cortison.) FISCHER, F. (1952). *Ugeskr. Laeg.*, **114**, 879. 16 refs.

Two Years' Experience with a Personal Preparation of Corticotrophin. (Deux ans d'expérience thérapeutique avec une préparation personnelle de corticostimuline.) COSTE, F., DELBARRE, F., and MONTEIL, H. DU (1952). *Sem. Hôp. Paris*, **28**, 1753. 9 figs, 16 refs.

Other General Subjects

Soft Tissue Calcification, with Special Reference to its Occurrence in the "Collagen Diseases". WHEELER, C. E., CURTIS, A. C., CAWLEY, E. P., GREKIN, R. H., and ZHEUTLIN, B. (1952). *Ann. intern. Med.*, **36**, 1050. 14 figs, bibl.

The authors discuss the causes of calcification in soft tissues, and decry the use of the terms "calcinosis circumscripta" to signify calcification in the region of joints and "calcinosis universalis" to indicate generalized calcification in subcutaneous tissues, muscles, and tendons. They suggest a new classification:

(1) Calcification due to tissue injury: (*a*) local; (*b*) associated with widespread disease of unknown aetiology.

(2) Calcification due to abnormality of calcium and/or phosphorus metabolism.

In reporting twelve cases, two fully and ten summarily, from the records of the University of Michigan Hospital, Ann Arbor, and reviewing them together with 54 cases reported in the literature since 1938, the authors found that if cases associated with a primary disturbance of calcium and phosphorus metabolism were excluded, dermatomyositis and scleroderma each accounted for 24 cases, and conditions such as rheumatoid arthritis and lupus erythematosus for only one or two cases each. They recommend the rejection of the term "idiopathic calcinosis" and suggest that the true diagnosis should read either dermatomyositis with calcinosis circumscripta, or scleroderma or Raynaud's syndrome with calcinosis universalis. In reviewing the metabolic findings the present authors, like previous workers, found no evidence of gross or of consistent abnormality in the blood chemistry or in the calcification of the bones, even in elderly female patients who might have been expected to show some degree of osteoporosis. The prognosis was best in scleroderma. The average age at onset for the primary disease was 31, and the average duration of the disease before reporting was 16·5 years. The areas of calcification tended to be small and localized to the hands, feet, elbows, knees, and pelvic region; females were predominantly affected. In the case of dermatomyositis average age at onset of the primary disease was fifteen, and the duration before reporting 7·5 years; females were affected twice as often as males, and the areas of calcification were more severe and more widespread than those of scleroderma. No form of treatment was of any avail in either group. The paper includes a useful table of differential diagnoses.

R. E. Tunbridge.

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